Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	138	phosphatidic acid phosphatase$1 or phosphatidate phosphohydrolase$1	US-PGPUB; USPAT	ADJ	OFF	2005/06/01 09:11
L2	45	1 near8 (human or isolat$ or purif$10 or gene$1 or sequence$1)	US-PGPUB; USPAT	ADJ	OFF	2005/06/01 09:13

4/17/97

PGPUB-DOCUMENT-NUMBER: 20050108789

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20050108789 A1

TITLE: Phosholipases, nucleic acids encoding them and methods for making and using them

PUBLICATION-DATE: May 19, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gramatikova, Svetlana	San Diego	CA	US	
Hazlewood, Geoff	San Diego	CA	US	
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APPL-NO: 10/ 796907

DATE FILED: March 8, 2004

RELATED-US-APPL-DATA:

child 10796907 A1 20040308

parent continuation-in-part-of 10421654 20030421 US PENDING

non-provisional-of-provisional 60374313 20020419 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
WO	PCT/US03/12556	2003WO-PCT/US03/12556	April 21, 2003

US-CL-CURRENT: 800/281, 435/196 , 435/419 , 435/468 , 435/69.1 , 536/23.2

ABSTRACT:

The invention provides novel polypeptides having phospholipase activity, including, e.g., phospholipase A, B, C and D activity, patatin activity, lipid acyl hydrolase (LAH) activity, nucleic acids encoding them and antibodies that bind to them. Industrial methods, e.g., oil degumming, and products comprising use of these phospholipases are also provided.

RELATED APPLICATIONS

[0001] This application is a continuation-in-part application ("CIP") of U.S. patent applications Ser. No. ("U.S. Ser. No.") 10/421,654, filed Apr. 21, 2003, which claims the benefit of priority under 35 U.S.C. .sctn. 119(e) of U.S. Provisional Application No. 60/374,313, filed Apr. 19, 2002; and, Patent Convention Treaty (PCT) International Application Serial No. PCT/US03/12556, filed Apr. 21, 2003. Each of the aforementioned applications is explicitly incorporated herein by reference in its entirety and for all purposes.

---------- KWIC ---------

Detail Description Paragraph - DETX (257):

[0361] The invention provides fusion of N-terminal or C-terminal subsequences of enzymes of the invention (e.g., signal sequences, prepro sequences) with other polypeptides, active proteins or protein fragments. The production of an enzyme of the invention (e.g., a phospholipase C enzyme) may also be accomplished by expressing the enzyme as an inactive fusion protein that is later activated by a proteolytic cleavage event (using either an endogenous or exogenous protease activity, e.g. trypsin) that results in the separation of the fusion protein partner and the mature enzyme, e.g., phospholipase C enzyme. In one aspect, the fusion protein of the invention is expressed from a hybrid nucleotide construct that encodes a single open reading frame containing the following elements: the nucleotide sequence for the fusion protein, a linker sequence (defined as a nucleotide sequence that encodes a flexible amino acid sequence that joins two less flexible protein domains), protease cleavage recognition site, and the mature enzyme (e.g., any enzyme of the invention, e.g., a phospholipase) sequence. In alternative aspects, the fusion protein can comprise a pectate lyase sequence, a xylanase sequence, a phosphatidic acid phosphatase sequence, or another sequence, e.g., a sequence that has previously been shown to be over-expressed in a host system of interest. Any host system can be used (see discussion, above), for example, E. coli or Pichia pastoris. The arrangement of the nucleotide sequences in the chimeric nucleotide construction can be determined based on the protein expression levels achieved with each fusion construct. Proceeding from the 5' end of the nucleotide construct to the 3' prime end of the construct, in one aspect, the nucleotide sequences is assembled as follows: Signal sequence/fusion protein/linker sequence/protease cleavage recognition site/mature enzyme (e.g., any enzyme of the invention, e.g., a phospholipase) or Signal sequence/pro sequence/mature enzyme/linker sequence/fusion protein. The expression of enzyme (e.g., any enzyme of the invention, e.g., a phospholipase) as an inactive fusion protein may improve the overall expression of the enzyme's sequence, may reduce any potential toxicity associated with the overproduction of active enzyme and/or may increase the shelf life of enzyme prior to use because enzyme would be inactive until the fusion protein e.g. pectate lyase is separated from the enzyme, e.g., phospholipase protein.

PGPUB-DOCUMENT-NUMBER: 20050096458

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20050096458 A1

TITLE: Full-length human cDNAs encoding potentially secreted proteins

PUBLICATION-DATE: May 5, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Dumas Milne Edwards, Jean-Baptiste	Paris		FR	
	Petit Lancy		CH	
Bougueleret, Lydie	Paris		FR	
Jobert, Severin				

APPL-NO: 10/ 643836

DATE FILED: August 19, 2003

RELATED-US-APPL-DATA:

child 10643836 A1 20030819

parent division-of 09731872 20001207 US ABANDONED

non-provisional-of-provisional 60169629 19991208 US

non-provisional-of-provisional 60187470 20000306 US

US-CL-CURRENT: 530/350

ABSTRACT:

The invention concerns GENSET polynucleotides and polypeptides. Such GENSET products may be used as reagents in forensic analyses, as chromosome markers, as tissue/cell/organelle-specific markers, in the production of expression vectors. In addition, they may be used in screening and diagnosis assays for abnormal GENSET expression and/or biological activity and for screening compounds that may be used in the treatment of GENSET-related disorders.

RELATED APPLICATION

[0001] The present application is a divisional of U.S. application Ser. No. 09/731,872, filed Dec. 7, 2000, which claims benefit, under 35 USC .sctn. 119(e), to the US Provisional Patent Applications Serial Nos. 60/169,629 and 60/187,470 filed Dec. 8, 1999, and Mar. 6, 2000, respectively, the disclosures of which are incorporated herein by reference in their entireties.

---------- KWIC ---------

Detail Description Paragraph - DETX (1426):

[1502] The protein of SEQ ID NO:399 is encoded by a cDNA that has homology to many forms of alternative splicing of PAP2 genes. For example, the protein of SEQ ID NO:399 has 29% homology with human phosphatidic acid phosphohydrolase

type-2C protein. The protein of SEQ ID NO:399 also has 40% homology with human phosphatidic acid phosphatase 2B protein. In addition, the protein of SEQ ID NO:399 has 33% homology with human type 2 phosphatidic acid phosphatase alpha-2 protein. PAP2-alpha2 is one of the two isoforms with PAP2-alpha1, presumed to be alternative splice variants from a single gene.

Detail Description Paragraph - DETX (1427):

[1503] Northern analysis has shown that PAP2-alpha mRNA expression was suppressed in several tumor tissues, indicating that PAP-2 may act as a tumor suppressor. The relationship of PAP and tumor suppression is further evidenced in findings that PAP activity is lower in fibroblast cell lines transformed with either the ras orfps oncogene than in the parental rat1 cell line (Brindley et al; Chem. Phys. Lipids 80 : 45-57 ; 1996, the disclosure of which is incorporated herein by reference in its entirety). As discussed above, a decrease in PAP activity in transformed cells correlates with a concomitant increase in PA concentration. Moreover, elevated PAP activity and lower levels of PA have been observed in contact-inhibited fibroblasts relative to proliferating and transformed fibroblasts (Brindley et al; Chem. Phys. Lipids 80: 45-57;1996, the disclosure of which is incorporated herein by reference in its entirety). Therefore, the protein of SEQ ID NO:399 or fragments thereof may be used to decrease cell division and as such can provide a useful tool in treating cancer. Subsequent analysis of colon tumor tissue derived from four donors confirmed lower expression of PAP2-alpha than in matching normal colon tissue. Considering these data and previous demonstrations that certain transformed cell lines have lower PAP activity, human PAP cDNAs may be used for gene therapy for certain tumors (Leung D. W., Tompkins C. K., White T.; DNA Cell Biol. 17: 377-385 (1998), the disclosure of which is incorporated herein by reference in its entirety). Accordingly, one embodiment of the present invention is the use of the protein of SEQ ID NO:399 or a fragment thereof as a tumor suppressor. For example, a nucleic acid expressing the protein of SEQ ID NO:399 or a fragment thereof may be introduced into an individual suffering from cancer in order to ameliorate or eliminate the cancer. In fact, nucleic acids encoding human phosphatidic acid phosphatases have been used to regulate levels of lipid cellular mediators and in gene therapy of e.g. cancer (PCT publication WO98/46730, the disclosure of which is incorporated herein by reference in its entirety).

Detail Description Paragraph - DETX (1428):

[1504] In another embodiment of the present invention, the protein of SEQ ID NO:399 or a fragment thereof can be used to control the balance of lipid mediators of cellular activation and signal transduction. The protein of the invention has 33% homology with human phosphatidic acid phosphatase 2A protein. PAP2A is an integral membrane glycoprotein at the cell surface that plays an active role in the hydrolysis and uptake of lipids from the extracellular space (Roberts R Z, Morris A J; Biochim Biophys Acta 2000 Aug. 24;1487(1):33-49, the disclosure of which is incorporated herein by reference in its entirety). Accordingly, the level or activity of the protein of SEQ ID NO:399 may be modulated to influence the rate or extent of hydrolysis and uptake of lipids from the extracellular space using methods such as those described herein.

PGPUB-DOCUMENT-NUMBER: 20050002904

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20050002904 A1

TITLE: Uses of vascular endothelial growth factor and type I collagen inducible protein (VCIP)

PUBLICATION-DATE: January 6, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wary, Kishore K.	Houston	TX	US	
Humtsoe, Joseph O.	Houston	TX	US	

APPL-NO: 10/ 812238

DATE FILED: March 29, 2004

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60485164 20030703 US

US-CL-CURRENT: 424/93.2, 514/44

ABSTRACT:

Vascular endothelial growth factor and type I collagen inducible protein (VCIP), also known as phosphatidic acid phosphatase 2b (PAP2b), was identified in a functional assay of angiogenesis. Previously, VCIP was not known to function as an integrin ligand. The present invention discloses VCIP-derived peptides and proteins act as integrin ligands. Since VCIP-derived peptides or proteins are capable of inhibiting specific cell-cell interactions, such inhibitors of cell-cell interactions would be useful for developing novel therapeutic approaches to treat diseases where these interactions have clear pathological consequences. For example, VCIP/PAP2b can be a novel target for anti-angiogenic, anti-cancer and anti-metastatic therapy.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This non-provisional patent application claims benefit of provisional patent application U.S. Ser. No. 60/458,164, filed Mar. 27, 2003, now abandoned.

---------- KWIC --------

Detail Description Paragraph - DETX (145):
[0157] Kai et al., Cloning and characterization of two human isozymes of Mg.sup.2+-independent phosphatidic acid phosphatase. J. Biol. Chem. 272:24572-24578 (1997).

PGPUB-DOCUMENT-NUMBER: 20040152092

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040152092 A1

TITLE: Regulation of human phosphatidic acid phosphatase type 2c-like protein

PUBLICATION-DATE: August 5, 2004

US-CL-CURRENT: 435/6, 435/196 , 435/320.1 , 435/325 , 435/69.1 , 536/23.2

APPL-NO: 10/ 476232

DATE FILED: October 29, 2003

PCT-DATA:
APPL-NO: PCT/EP02/05045
DATE-FILED: May 8, 2002
PUB-NO:
PUB-DATE:
371-DATE:
102(E)-DATE:

PGPUB-DOCUMENT-NUMBER: 20040133944

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040133944 A1

TITLE: Seed oil suppression to enhance yield of commercially important macromolecules

PUBLICATION-DATE: July 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hake, Kater Davis	Cleveland	MS	US	
Kerby, Thomas Arthur	Greenville	MS	US	
Collins, Harry Benjamin	Scott	MS	US	
Keim, Don Lee	Leland	MS	US	

APPL-NO: 10/ 647140

DATE FILED: August 25, 2003

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60438500 20030108 US

US-CL-CURRENT: 800/281

ABSTRACT:

This invention relates to a method for making a genetically modified cotton plant by regenerating a whole plant from a plant cell that has been transfected with DNA sequences including a gene, the expression of which results in suppression of oil biosynthesis in the developing seed. Plants made according to this method exhibit increased production of fiber. Also disclosed is a method for making a non-genetically modified cotton plant with reduced seed-oil content by selecting native alleles or alleles produced through mutagenesis that result in reduced oil content with resulting enhanced fiber yield. Methods are disclosed for developing commercially acceptable cultivars that contain the cottonseed-oil suppression trait. Plant cells, plant tissues, plant seed and whole plants containing the above DNA sequences and alleles form part of the invention.

[0001] This application claims the benefit of co-pending U.S. provisional application Serial No. 60/438,500, filed Jan. 8, 2003.

---------- KWIC ---------

Detail Description Paragraph - DETX (14):

[0047] An earlier enzyme in the biosynthetic pathway of TAG, lysophosphatidic acid acyltransferase (LPAT), also regulates TAG production in Arabidopsis thaliana and Brassica napus (Zou et al., 1997). The sequence of the penultimate enzyme in the formation of TAG, phosphatidic acid phosphatase (PAP), has been reported (Lassner, 2002). PAP dephosphorylates the sn-3 position of phosphatidic acid to form sn-1,2-diacylglycerol, the precursor of

TAG. Lassner (2002) has claimed that use of sense and antisense sequences of PAP to increase and decrease TAG in corn and soybeans produces plants with altered lipid composition and total lipid levels. Although most of the current work in oil biosynthetic manipulation has been focused on increasing oil content, such as the work with LPAT, downregulation of a pathway generally is considered to require less genetic manipulation than upregulation, where the biosynthesis of precursor molecules also must be upregulated (Taylor, 1998).

PGPUB-DOCUMENT-NUMBER: 20040110221

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040110221 A1

TITLE: Methods for diagnosing RCC and other solid tumors

PUBLICATION-DATE: June 10, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Twine, Natalie C.	Goffstown	NH	US	
Burczynski, Michael E.	Swampscott	MA	US	
Trepicchio, William L.	Andover	MA	US	
Dorner, Andrew J.	Lexington	MA	US	
Stover, Jennifer A.	Topsfield	MA	US	
Slonim, Donna K.	North Andover	MA	US	

APPL-NO: 10/ 717597

DATE FILED: November 21, 2003

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60427982 20021121 US

non-provisional-of-provisional 60459782 20030403 US

US-CL-CURRENT: 435/6, 435/7.23

ABSTRACT:

Methods, systems and equipment for diagnosing renal cell carcinoma (RCC) and other solid tumors. This invention identifies numerous disease genes that are differentially expressed in the peripheral blood of patients having RCC or other solid tumors relative to disease-free humans. These disease genes can be used as surrogate markers for detecting the presence or absence of RCC or other solid tumors.

[0001] This application incorporates by reference the entire disclosure of U.S. Provisional Application Serial No. 60/427,982, filed Nov. 21, 2002 and entitled "Methods for Diagnosing RCC and/or Solid Tumors." This application also incorporates by reference the entire disclosure of U.S. Provisional Application Serial No. 60/459,782, filed Apr. 3, 2003 and entitled "Methods for Diagnosing RCC and/or Solid Tumors." In addition, this application incorporates by reference all materials recorded in compact discs "Copy 1" and "Copy 2." Each of the compact discs includes the sequence listing file entitled "AM101080L Sequence Listing.ST25.txt" (2,206 KB, created on Nov. 20, 2003).

---------- KWIC ---------

Detail Description Paragraph - DETX (134):
[0171] CPS 65 corresponds to PPAP2B which encodes phosphatidic acid phosphatase type 2B. The gene has LocusID: 8613, and is located on chromosome

1 with reported cytogenetic location 1pter-p22.1. The gene product is magnesium-independent phosphatidic acid phosphatase 2b. It can convert phosphatidic acid to diacylglycerol. It can also hydrolyze lysophosphatidate, ceramide-1-phosphate, and sphingosine-1-phosphate.

PGPUB-DOCUMENT-NUMBER: 20040110197

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040110197 A1

TITLE: Method of determining tumor characteristics by determining abnormal copy number or expression level of lipid-associated genes

PUBLICATION-DATE: June 10, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Skinner, Michael K.	Pullman	WA	US	
Patton, Jodi L.	Pullman	WA	US	

APPL-NO: 10/ 647426

DATE FILED: August 26, 2003

RELATED-US-APPL-DATA:

child 10647426 A1 20030826

parent continuation-of 09676052 20000928 US ABANDONED

US-CL-CURRENT: 435/6

ABSTRACT:

A method of assessing tumor characteristics in tissue samples by determining the copy number or expression level of genes associated with lipid metabolism, synthesis, or action is provided. Gene copy number may be assessed directly from chromosomal material or by determining the expression level of the gene in a tissue sample. The use of physical platforms comprising immobilized nucleic acid polymers to determine copy number or expression level of lipid associated genes by hybridization techniques is also provided.

---------- KWIC ---------

Brief Description of Drawings Paragraph - DRTX (23):
[0069] SEQ ID NO. 20: The sequence of the cDNA coding for Phosphatidic Acid Phosphatase type 2b.

Brief Description of Drawings Paragraph - DRTX (24):
[0070] SEQ ID NO. 21: The sequence of the cDNA coding for Phosphatidic Acid Phosphatase type 2a.

Brief Description of Drawings Paragraph - DRTX (28):
[0074] SEQ ID NO. 25: The sequence of the cDNA coding for Phosphatidic Acid Phosphatase type 2c.

PGPUB-DOCUMENT-NUMBER: 20040096841

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040096841 A1

TITLE: Novel polypeptide-phosphatidic acid phsphatase 29.81 and the polynucleotide encoding said polypeptide

PUBLICATION-DATE: May 20, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mao, Yumin	Shanghai		CN	
Xie, Yi	Shanghai		CN	

APPL-NO: 10/ 362239

DATE FILED: February 21, 2003

PCT-DATA:
APPL-NO: PCT/CN01/01253
DATE-FILED: Aug 20, 2001
PUB-NO:
PUB-DATE:
371-DATE:
102(E)-DATE:

US-CL-CURRENT: 435/6, 435/196 , 435/320.1 , 435/325 , 435/69.1 , 530/388.26 , 536/23.2

ABSTRACT:

The invention disclosed a new kind of polypeptide-phosphatidic acid phosphatase 29.81 and the polynucleotide encoding said polypeptide and a process for priducing the polypeptide by DNA recombinant methods. It also disclosed the method of applying the polypeptide for the treatment of various kinds of diseases, such as peripheral nervous demyelination, night blindness, rachitis, fatty liver, bronchial asthma and peptic ulcer. The antagonist of the polypeptide and therapeutic use of the same is also disclosed. In addition, it refers to the use of polynucleotide encoding said phosphatidic acid phosphatase 29.81.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (2):
[0001] The invention relates to the field of biotechnology. In particular, the invention relates to a novel polypeptide, phosphatidic acid phosphatase 29.81, and a polynucleotide sequence encoding said polypeptide. The invention also relates to the method for the preparation and use of said polynucleotide and polypeptide.

Summary of Invention Paragraph - BSTX (14):
[0012] As described above, phosphatidate phosphatase 29.81 plays an essential role in the regulation of important biological functions such as cell division and embryogenesis, and it is believed that many proteins are involved

in these regulations. So the determination of those related phosphatidic acid phosphatase 29.81, especially of their amino acid sequences is always desired in this field. The isolation of this novel phosphatidic acid phosphatase 29.81 forms the basis for research of the protein function under normal and clinical conditions, and this protein can be used in disease diagnosis and/or drug development.

Summary of Invention Paragraph - BSTX (16):
[0013] One objective of the invention is to provide an isolated novel polypeptide, i.e., a phosphatidic acid phosphatase 29.81, and fragments, analogues and derivatives thereof.

Brief Description of Drawings Paragraph - DRTX (3):
[0035] FIG. 1 shows an alignment comparison of amino acid sequences of phosphatidic acid phosphatase 29.81 of the invention and phosphatidic acid phosphatase. The upper sequence is phosphatidic acid phosphatase 29.81, and the lower sequence is phosphatidic acid phosphatase. The identical and similar amino acids are indicated by a one-letter code of amino acid and "+" respectively.

Brief Description of Drawings Paragraph - DRTX (4):
[0036] FIG. 2 shows the SDS-PAGE of the isolated phosphatidic acid phosphatase 29.81 which has a molecular weight of 29.81 kDa. The isolated protein band is marked with an arrow.

Detail Description Paragraph - DETX (11):
[0046] "Substantially pure" refers to the condition of purity without any other natural related proteins, lipids, saccharides, or other substances. Ordinarily skilled artisans in this field can purify phosphatidic acid phosphatase 29.81 by standard protein purification techniques. Substantially pure phosphatidic acid phosphatase 29.81 produces a single main band in denaturing polyacrylamide gel. The purity of phosphatidic acid phosphatase 29.81 can also be analyzed by amino acid sequence analysis.

Detail Description Paragraph - DETX (23):
[0058] As used herein, "isolated phosphatidic acid phosphatase 29.81," means that phosphatidic acid phosphatase 29.81, does not essentially contain other proteins, lipids, carbohydrates or any other substances associated therewith in nature. Those skilled in the art can purify phosphatidic acid phosphatase 29.81, by standard protein purification techniques. The purified polypeptide forms a single main band on a non-reductive PAGE gel. The purity of phosphatidic acid phosphatase 29.81 can be analyzed by amino acid sequence analysis.

Detail Description Paragraph - DETX (24):
[0059] The invention provides a novel polypeptide-phosphatidic acid phosphatase 29.81, which comprises the amino acid sequence shown in SEQ ID NO: 2. The polypeptide of the invention may be a recombinant polypeptide, natural polypeptide, or synthetic polypeptide, preferably a recombinant polypeptide. The polypeptide of the invention may be a purified natural product or a chemically synthetic product. Alternatively, it may be produced from prokaryotic or eukaryotic hosts, such as bacterial, yeast, higher plant, insect, and mammalian cells, using recombinant techniques. Depending on the host used in the protocol of recombinant production, the polypeptide of the invention may be glycosylated or non-glycosylated. The polypeptide of the invention may or may not comprise the starting Met residue.

Detail Description Paragraph - DETX (33):
[0068] The invention also relates to nucleic acid fragments hybridized with the herein above sequence. As used in the present invention, the length of the "nucleic acid fragment" is at least more than 10 bp, preferably at least 20-30 bp, more preferably at least 50-60 bp, and most preferably at least 100 bp. The nucleic acid fragment can be used in amplification techniques of nucleic acid, such as PCR, so as to determine and/or isolate the polynucleotide encoding phosphatidic acid phosphatase 29.81.

Detail Description Paragraph - DETX (35):
[0070] According to the invention, the specific nucleic acid sequence encoding phosphatidic acid phosphatase 29.81 can be obtained in various ways. For example, the polynucleotide is isolated by hybridization techniques well-known in the art, which include, but are not limited to 1) the hybridization between a probe and genomic or cDNA library so as to select a homologous polynucleotide sequence, and 2) antibody screening of expression library so as to obtain polynucleotide fragments encoding polypeptides having common structural features.

Detail Description Paragraph - DETX (38):
[0073] Numerous well-known methods can be used for screening for the polynucleotide of the invention from cDNA library. These methods include, but are not limited to, (1) DNA-DNA or DNA-RNA hybridization; (2) the appearance or loss of the function of the marker-gene; (3) the determination of the level of phosphatidic acid phosphatase 29.81 transcripts; (4) the determination of protein product of gene expression by immunology methods or the biological activity assays. The above methods can be used alone or in combination.

Detail Description Paragraph - DETX (40):
[0075] In method (4), the detection of the protein products expressed by phosphatidic acid phosphatase 29.81 gene can be carried out by immunological methods, such as Western blotting, radioimmunoassay, and ELISA.

Detail Description Paragraph - DETX (43):
[0078] The invention further relates to a vector comprising the polynucleotide of the invention, a genetically engineered host cell transformed with the vector of the invention or directly with the sequence encoding phosphatidic acid phosphatase 29.81, and a method for producing the polypeptide of the invention by recombinant techniques.

Detail Description Paragraph - DETX (44):
[0079] In the present invention, the polynucleotide sequences encoding phosphatidic acid phosphatase 29.81 may be inserted into a vector to form a recombinant vector containing the polynucleotide of the invention. The term "vector" refers to a bacterial plasmid, bacteriophage, yeast plasmid, plant virus or mammalian virus such as adenovirus, retrovirus or any other vehicle known in the art. Vectors suitable for use in the present invention include, but are not limited to the T7-based expression vector for expression in bacteria (Rosenberg, et al., Gene, 56: 125, 1987), The pMSXND expression vector for expression in mammalian cells (Lee and Nathans, J. Biol. Chem., 263: 3521, 1988) and baculovirus-derived vectors for expression in insect cells. Any plasmid or vector can be used to construct the recombinant expression vector as long as it can replicate and is stable in the host. One important feature of an expression vector is that the expression vector typically contains an origin of replication, a promoter, a marker gene as well as translation regulatory components.

Detail Description Paragraph - DETX (45):
[0080] Methods known in the art can be used to construct an expression

vector containing the DNA sequence of phosphatidic acid phosphatase 29.81 and appropriate transcription/translation regulatory components. These methods include in vitro recombinant DNA technique, DNA synthesis technique, in vivo recombinant technique and so on (Sambroook, et al. Molecular Cloning, a Laboratory Manual, cold Spring Harbor Laboratory. New York, 1989). The DNA sequence is operatively linked to a proper promoter in an expression vector to direct the synthesis of mRNA. Exemplary promoters are lac or trp promoter of E. coli; PL promoter of A phage; eukaryotic promoters including CMV immediate early promoter, HSV thymidine kinase promoter, early and late SV40 promoter, LTRs of retrovirus, and other known promoters which control gene expression in the prokaryotic cells, eukaryotic cells or viruses. The expression vector may further comprise a ribosome binding site for initiating translation, transcription terminator and the like. Transcription in higher eukaryotes is increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp in length that act on a promoter to increase gene transcription level. Examples include the SV40 enhancer on the late side of the replication origin 100 to 270 bp, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

Detail Description Paragraph - DETX (51):
[0086] (1) transfecting or transforming the appropriate host cells with the polynucleotide (or variant) encoding human phosphatidic acid phosphatase 29.81 of the invention or the recombinant expression vector containing said polynucleotide;

Detail Description Paragraph - DETX (75):
[0110] Monoclonal antibodies specific to phosphatidic acid phosphatase 29.81 can be labeled by radioactive isotopes, and injected into human body to trace the location and distribution of phosphatidic acid phosphatase 29.81. This radioactively labeled antibody can be used in the non-wounding diagnostic method for the determination of tumor location and metastasis.

Detail Description Paragraph - DETX (80):
[0115] New phosphatidic acid phosphatase 29.81 polynucleotides also have many therapeutic applications. Gene therapy technology can be used in the therapy of abnormal cell proliferation, development or metabolism, which are caused by the loss of phosphatidic acid phosphatase 29.81 expression or the abnormal or non-active expression of phosphatidic acid phosphatase 29.81. Recombinant gene therapy vectors, such as virus vectors, can be designed to express mutated phosphatidic acid phosphatase 29.81 so as to inhibit the activity of endogenous phosphatidic acid phosphatase 29.81. For example, one form of mutated phosphatidic acid phosphatase 29.81 is a truncated phosphatidic acid phosphatase 29.81 whose signal transduction domain is deleted. Therefore, this mutated phosphatidic acid phosphatase 29.81 can bind the downstream substrate without the activity of signal transduction. Thus, the recombinant gene therapy vectors can be used to cure diseases caused by abnormal expression or activity of phosphatidic acid phosphatase 29.81. The expression vectors derived from a virus, such as retrovirus, adenovirus, adenoassociated virus, herpes simplex virus, parvovirus, and so on, can be used to introduce the phosphatidic acid phosphatase 29.81 gene into the cells. The methods for constructing a recombinant virus vector harboring phosphatidic acid phosphatase 29.81 gene are described in the literature (Sambrook, et al. supra). In addition, the recombinant phosphatidic acid phosphatase 29.81 gene can be packed into liposome and then transferred into the cells.

Detail Description Paragraph - DETX (83):
[0118] The polynucleotide encoding phosphatidic acid phosphatase 29.81 can be used in the diagnosis of phosphatidic acid phosphatase 29.81 related diseases. The polynucleotide encoding phosphatidic acid phosphatase 29.81 can

be used to detect whether phosphatidic acid phosphatase 29.81 is expressed or not, and whether the expression of phosphatidic acid phosphatase 29.81 is normal or abnormal in the case of diseases. For example, phosphatidic acid phosphatase 29.81 DNA sequences can be used in the hybridization with biopsy samples to determine the expression of phosphatidic acid phosphatase 29.81. The hybridization methods include Southern blotting, Northern blotting and in situ blotting, etc., which are well-known and established techniques. The corresponding kits are commercially available. A part of or all of the polynucleotides of the invention can be used as probe and fixed on a microarray or DNA chip for analysis of differential expression of genes in tissues and for the diagnosis of genes. The phosphatidic acid phosphatase 29.81 specific primers can be used in RNA-polymerase chain reaction and in vitro amplification to detect transcripts of phosphatidic acid phosphatase 29.81.

Detail Description Paragraph - DETX (84):
[0119] Further, detection of mutations in phosphatidic acid phosphatase 29.81 gene is useful for the diagnosis of phosphatidic acid phosphatase 29.81-related diseases. Mutations of phosphatidic acid phosphatase 29.81 include site mutation, translocation, deletion, rearrangement and any other mutations compared with the wild-type phosphatidic acid phosphatase 29.81 DNA sequence. The conventional methods, such as Southern blotting, DNA sequencing, PCR and in situ blotting, can be used to detect a mutation. Moreover, mutations sometimes affects the expression of protein. Therefore, Northern blotting and Western blotting can be used to indirectly determine whether the gene is mutated or not.

Detail Description Paragraph - DETX (97):
Cloning of Phosphatidic Acid Phosphatase 29.81 Gene

Detail Description Paragraph - DETX (101):
[0131] The homology research of the DNA sequence and its protein sequence of phosphatidic acid phosphatase 29.81 of the invention were performed by Blast (Basic local Alignment search tool) (Altschul, S F et al. J. Mol. Biol., 1990; 215: 403-10) in databases such as Genbank, Swissport, etc. The most homologous gene to phosphatidic acid phosphatase 29.81 of the invention is known phosphatidic acid phosphatase. The Genbank accession number of its encoded protein is AC006200. The alignment result of the protein was shown in FIG. 1. Two proteins are highly homologous with an identity of 36% and a similarity of 57%.

Detail Description Paragraph - DETX (103):
Cloning Phosphatidic Acid Phosphatase 29.81 Gene by RT-PCR

Detail Description Paragraph - DETX (109):
Northern Blotting of Expression of Phosphatidic Acid Phosphatase 29.81 Gene

Detail Description Paragraph - DETX (110):
[0136] Total RNA was extracted by one-step method (Anal. Biochem 1987, 162, 156-159) with guanidinium isocyanate-phenol-chloroform. That is, homogenate the organize using 4 M guanidinium isocyanate-25 mM sodium citrate, 0.2 M sodium acetate (pH 4.0), add 1 volume phenol and 1/5 volume chloroform-isoamyl alcohol (49:1), centrifuge after mixing. Take out the water phase, add 0.8 volume isopropyl alcohol, then centrifuge the mixture. Wash the RNA precipitation using 70% ethanol, then dry, then dissolve it in the water. 20 .mu.g RNA was electrophoresed on the 1.2% agarose gel containing 20 mM 3-(N-morpholino) propane sulfonic acid. (pH 7.0)--5 mM sodium acetate-imM EDTA--2.2 M formaldehyde. Then transfer it to a nitrocellulose filter. Prepare the .sup.32P-labelled DNA probe with .alpha.-.sup.32P dATP by random primer method. The DNA probe used is the coding sequence (56 bp-871 bp) of

phosphatidic acid phosphatase 29.81 amplified by PCR indicated in FIG. 1. The nitrocellulose filter with the transferred RNA was hybridized with the .sup.32P-labelled DNA probe (2.times.10.sup.6 cpm/ml) overnight in a buffer containing 50% formamide--25 mM KH.sub.2PO.sub.4 (Ph 7.4)--5.times. Denhardt's solution and 200 .mu.g/ml salmine. Then wash the filter in the 1.times.SSC--0.1% SDS, at 55.degree. C., for 30 min. Then analyze and quantitative determinate using Phosphor Imager.

Detail Description Paragraph - DETX (112):
In Vitro Expression, Isolation and Purification of Recombinant Phosphatidic Acid Phosphatase 29.81

Detail Description Paragraph - DETX (114):
[0138] These two primers contain a NdeI and EcoRI cleavage site on the 5' end respectively. Within the sites are the coding sequences of the 5' and 3' end of the desired gene. NdeI and EcoRI cleavage sites were corresponding to the selective cleavage sites on the expression vector pET-28b (+) (Novagen, Cat. No. 69865.3). PCR amplification was performed with the plasmid pBS-2933e11 containing the full-length target gene as a template. The PCR reaction was subject to a 50 .mu.l system containing 10 pg pBS-2933e11 plasmid, 10 pmol of Primer-3 and 10 pmol of Primer-4, 1 .mu.l of Advantage polymerase Mix (Clontech). The parameters of PCR were 94.degree. C. 20 sec, 60.degree. C. 30 sec, and 68.degree. C. 2 min for 25 cycles. After digesting the amplification products and the plasmid pET-28 (+) by NdeI and EcoRI, the large fragments were recovered and ligated with T4 ligase. The ligated product was transformed into E. coli DH5.alpha. with the calcium chloride method. After cultured overnight on a LB plate containing a final concentration of 30 .mu.g/ml kanamycin, positive clones were selected out using colony PCR and then sequenced. The positive clone (pET-2933e11) with the correct sequence was selected out and the recombinant plasmid thereof was transformed into BL21 (DE3) plySs (Novagen) using the calcium chloride method. In a LB liquid medium containing a final concentration of 30 .mu.g/ml of kanamycin, the host bacteria BL21 (pET-2933e11) were cultured at 37.degree. C. to the exponential growth phase, then IPTG were added with the final concentration of 1 mmol/L, the cells were cultured for another 5 hours, and then centrifuged to harvest the bacteria. After the bacteria were sonicated, the supernatant was collected by centrifugation. Then the purified desired protein-phosphatidic acid phosphatase 29.81 was obtained by a His.Bind Quick Cartridge (Novagen) affinity column with binding 6His-Tag. SDS-PAGE showed a single band at 29.81 kDa (FIG. 2). The band was transferred onto the PVDF membrane and the N terminal amino acid was sequenced by Edams Hydrolysis, which shows that the first 15 amino acids on N-terminus were identical to those in SEQ ID NO: 2.

Detail Description Paragraph - DETX (117):
[0139] The following specific phosphatidic acid phosphatase 29.81 polypeptide was synthesized by a polypeptide synthesizer (PE-ABI): NH2-Met-Arg-Glu-Leu-Ala-Ile-Glu-Ile-Gly-Val-Arg-Ala-Leu-Leu-Phe-COOH (SEQ ID NO: 7). The polypeptide was conjugated with hemocyanin and bovine serum albumin (BSA) respectively to form two composites (See Avrameas et al., Immunochemistry, 1969, 6: 43). 4 mg of hemocyanin-polypeptide composite was used to immunize rabbit together with Freund's complete adjuvant. The rabbit was re-immunized with the hemocyanin-polypeptide composite and Freund's incomplete adjuvent 15 days later. The titer of antibody in the rabbit sera was determined with a titration plate coated with 15 .mu.g/ml BSA-polypeptide composite by ELISA. The total IgG was isolated from the sera of an antibody positive rabbit with Protein A-Sepharose. The polypeptide was bound to Sepharose 4B column activated by cyanogen bromide. The antibodies against the polypeptide were isolated from the total IgG by affinity chromatography. The immunoprecipitation approved that the purified antibodies could specifically

bind to phosphatidic acid phosphatase 29.81.

Claims Text - CLTX (2):
1. An isolated polypeptide-phosphatidic acid phosphatase 29.81 comprising a polypeptide having the amino acid sequence of SEQ ID NO: 2, its active fragments, analogues and derivatives.

Claims Text - CLTX (10):
9. A method for producing a polypeptide having the activity of phosphatidic acid phosphatase 29.81, which comprises the steps of: (a) culturing the engineered host cell of claim 8 under the conditions suitable for expression of phosphatidic acid phosphatase 29.81; (b) isolating the polypeptides having the activity of phosphatidic acid phosphatase 29.81 protein from the culture.

PGPUB-DOCUMENT-NUMBER: 20040039212

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040039212 A1

TITLE: Sphingolipid derivatives and their methods of use

PUBLICATION-DATE: February 26, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Merrill, Alfred H. JR.	Dunwoody	GA	US	
Keane, Thomas E.	Dunwoody	GA	US	
Bhalla, Kapil N.	Atlanta	GA	US	
Schmelz, Eva M.	Atlanta	GA	US	

APPL-NO: 10/ 647801

DATE FILED: August 25, 2003

RELATED-US-APPL-DATA:

child 10647801 A1 20030825

parent continuation-of 09249211 19990212 US GRANTED

parent-patent 6610835 US

non-provisional-of-provisional 60074536 19980212 US

US-CL-CURRENT: 548/566, 549/491 , 549/74 , 554/36

ABSTRACT:

Derivatives of sphingolipids of the formula: 1
are provided wherein the substituents are as defined in the specification and wherein there is at least one R.sup.2 substituent in the sphingolipid derivative. The compounds are useful in the treatment of of abnormal cell proliferation, including benign and malignant tumors, the promotion of cell differentiation, the induction of apoptosis, the inhibition of protein kinase C, and the treatment of inflammatory conditions, psoriasis, inflammatory bowel disease as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissue. The invention also includes a method for triggering the release of cytochrome c from mitochondria that includes administering an effective amount of a sphingolipid or its derivative or prodrug to a host in need thereof. Further, the invention provides a method for treating bacterial infections, including those that influence colon cancer and other disorders of the intestine, that includes administering an effective amount of one of the active compounds identified herein.

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Summary of Invention Paragraph - BSTX (6):
[0006] The hydroxyl groups at positions 1, 3 and sometimes 4 or 6 are also relevant to the behavior of these compounds. This has mostly been considered

from the perspective of how hydrogen bonding in the interfacial region of the bilayer affects membrane structure (Thompson and Tillack, Annu. Biophys. Chem., 14:361-386, 1985). However, in a study of phosphatidic acid phosphatase purified from yeast (Wu et al., J. Biol. Chem. 268:13830-13837, 1993), inhibition of this enzyme by long-chain bases showed a considerable preference for phytosphingosine and sphinganine over sphingosine, which matches the types of sphingoid bases found in yeast. Therefore, these functional groups appear to be present both for structural purposes and to allow optimum interaction with cellular targets.

PGPUB-DOCUMENT-NUMBER: 20030207901

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030207901 A1

TITLE: Hydroxyl-containing compounds

PUBLICATION-DATE: November 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Underiner, Gail E.	Malvern	PA	US	
Porubek, David	Seattle	WA	US	
Klein, J. Peter	Vashon	WA	US	
Woodson, Paul	Bothel	WA	US	
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APPL-NO: 10/ 437298

DATE FILED: May 14, 2003

RELATED-US-APPL-DATA:

child 10437298 A1 20030514

parent division-of 09361145 19990727 US PENDING

US-CL-CURRENT: 514/263.36, 514/251 , 514/266.3 , 514/308 , 514/415

ABSTRACT:

Disclosed are therapeutic compounds having the formula:
(R).sub.j-(CORE MOIETY),
including resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is a bicyclic ring structure having at least one heterocyclic ring that contains five to six ring atoms and up to two nitrogen heteroatoms. R is selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, C.sub.1-6 alkyl or C.sub.1-6 alkenyl, and at least one R has the formula I: 1
n is an integer from 1 to 20, at least one of X or Y is --OH. Another of X or Y, which is not --OH, is hydrogen, CH.sub.3--, CH.sub.3--CH.sub.2--, CH.sub.3--(CH.sub.2).sub.2-- or (CH.sub.3).sub.2--CH.sub.2--, and each W.sub.1, W.sub.2, and W.sub.3 is independently hydrogen, CH.sub.3--, CH.sub.3--CH.sub.2--, CH.sub.3--(CH.sub.2).sub.2-- or (CH.sub.3).sub.2--CH.sub.2--. The X, Y, W.sub.1, W.sub.2, or W.sub.3 alkyl groups may be unsubstituted or substituted by an hydroxyl, halo or dimethylamino group. The disclosed compounds and therapeutic compositions thereof are useful in treating individuals having a disease or treatment-induced toxicity, mediated by second messenger activity.

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. application Ser. No. 08/756,703, filed Nov. 26, 1996, and U.S. application Ser. No.

09/288,556, filed Apr. 9, 1999. U.S. application Ser. No. 08/756,703 is a continuation of U.S. application Ser. No. 08/153,356, filed Nov. 16, 1993, which is a continuation-in-part of U.S. application Ser. No. 07/976,353, filed Nov. 16, 1992. U.S. application Ser. No. 09/288,556 is a continuation-in-part of U.S. application Ser. No. 09/008,020, which was filed Jan. 16, 1998. The disclosures of the aforementioned applications are incorporated by reference herein in their entirety.

---------- KWIC --------

Detail Description Paragraph - DETX (45):

[0074] IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

PGPUB-DOCUMENT-NUMBER: 20030157513

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030157513 A1

TITLE: Novel triacylgl ycerol biosynthesis in the cytosol of eukaryotes

PUBLICATION-DATE: August 21, 2003

INVENTOR-INFORMATION:
NAME CITY STATE COUNTRY RULE-47
Rajasekharan, Ram Karnataka IN

APPL-NO: 10/ 230331

DATE FILED: August 29, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60315757 20010830 US

US-CL-CURRENT: 435/6, 435/193 , 435/198 , 435/254.2 , 435/320.1 , 435/325 , 435/366 , 435/7.1 , 514/44 , 536/23.2

ABSTRACT:

This invention describes novel catalytically active cytosolic enzymes for triacylglycerol biosynthesis from eukaryotic systems. The complex from oleaginous yeast was enzymatically characterized, and was found to contain lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl-acyl carrier protein synthetase, superoxide dismutase and acyl carrier protein. The triacylglycerol biosynthetic machinery rapidly incorporates free fatty acids as well as fatty acyl-coenzyme A into triacylglycerol and its biosynthetic intermediates. Lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase and diacylglycerol acyltransferase from the complex were microsequenced. Acyl carrier protein, superoxide dismutase and diacylglycerol acyltransferase genes were cloned and expressed in bacterial system. The soluble triacylglycerol biosynthetic enzymes (lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase) in yeast, rat adipocytes and human hepatocyte cell-line (HepG2) exist in the cytosol either as free enzymes or as a multienzyme complex.

---------- KWIC ---------

Abstract Paragraph - ABTX (1):

This invention describes novel catalytically active cytosolic enzymes for triacylglycerol biosynthesis from eukaryotic systems. The complex from oleaginous yeast was enzymatically characterized, and was found to contain lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl-acyl carrier protein synthetase, superoxide dismutase and acyl carrier protein. The triacylglycerol biosynthetic machinery rapidly incorporates free fatty acids as well as fatty acyl-coenzyme A into triacylglycerol and its biosynthetic intermediates. Lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase and

diacylglycerol acyltransferase from the complex were microsequenced. Acyl carrier protein, superoxide dismutase and diacylglycerol acyltransferase genes were cloned and expressed in bacterial system. The soluble triacylglycerol biosynthetic enzymes (lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase) in yeast, rat adipocytes and human hepatocyte cell-line (HepG2) exist in the cytosol either as free enzymes or as a multienzyme complex.

Summary of Invention Paragraph - BSTX (2):

[0001] This invention relates to novel catalytically active cytosolic enzymes for triacylglycerol biosynthesis from eukaryotic systems. The complex from oleaginous yeast was enzymatically characterized and was found to contain lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl-acyl carrier protein synthetase, superoxide dismutase and acyl carrier protein. The triacylglycerol biosynthetic machinery rapidly incorporates free fatty acids as well as fatty acyl-coenzyme A into triacylglycerol and its biosynthetic intermediates. Lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase and diacylglycerol acyltransferase from the complex were microsequenced. Acyl carrier protein, superoxide dismutase and diacylglycerol acyltransferase genes were cloned and expressed in bacterial system. The triacylglycerol biosynthetic enzymes such as lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase and diacylglycerol acyltransferase in baker's yeast, rat adipocytes and human hepatocyte cell-line can exist in the cytosol as free enzymes.

Summary of Invention Paragraph - BSTX (7):

[0005] TAG enzymes in yeast comprise of lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl-acyl carrier protein synthetase and acyl carrier protein. These TAG biosynthetic enzymes may exist as either free or multienzyme complex. Among these enzymes, lysophosphatidic acid acyltransferase can be identified in any yeast strain by immunological cross reactivity to the peptide sequence ALELQADDFNK (peptide SEQ ID 2), diacylglycerol acyltransferase identified by immunological cross reactivity to the peptide sequence XLWAVVGAQPFGGARGS (peptide SEQ ID 7) and phosphatidic acid phosphatase identified by immunological cross reactivity to peptides NALTGLHMGGGK (peptide SEQ ID 4) and YVEGARP (peptide SEQ ID 6). TAG biosynthetic enzymes thus isolated from oleaginous yeast can utilize free fatty acids or fatty acyl-CoA or acyl-ACP as substrates.

Summary of Invention Paragraph - BSTX (21):

[0017] In the invention, the soluble TAG enzymes in yeast comprise lysophosphatidic acid acyltransferase with peptide SEQ ID 1 XALELQADDFNK and peptide SEQ ID 3 XXVNNVXPGXIEQ, phosphatidic acid phosphatase with peptide SEQ ID 4 NALTGLHMGGGK and peptide SEQ ID 5 YVEGARPXK, diacylglycerol acyltransferase with peptide SEQ ID 7 XLWAVVGAQPFGGARGS, acyl-acyl carrier protein synthetase with peptide SEQ ID 8 VHLAVALYGLAAVRVSRIVR, superoxide dismutase encoded by the gene sequence as in SEQ ID 9, and acyl carrier protein encoded by the gene sequence as in SEQ ID 10. The gene sequence encoding superoxide dismutase and diacylglycerol acyltransferase acyl carrier protein have sequence homology to DNA sequences as in SEQ ID 9, SEQ ID 11 and SEQ ID 10, respectively. The lysophatidic acid acyltransferase is identified by immunological cross reactivity to the peptide sequence ALELQADDFNK (as in peptide SEQ ID 2), diacylglycerol acyltransferase is identified by immunological cross reactivity to the pepetide sequence XLWAVVGAQPFGGARGS (as in peptide SEQ ID 7) and phosphatidic acid phosphatase is identified by immunological cross reactivity to peptides NALTGLHMGGGK (as in peptide SEQ ID 4) and YVEGARP (as in peptide SEQ ID 6).

Summary of Invention Paragraph - BSTX (27):
[0023] This invention provides purified polypeptides, which are lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein, acyl-ACP synthetase and superoxide dismutase.

Summary of Invention Paragraph - BSTX (35):
[0031] This invention provides a method for treating a subject who has an imbalance in triglyceride (triacylglycerol) levels due to a defect in the synthesis of soluble triglyceride, which comprises introducing the isolated nucleic acid which encodes lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein (ACP), acyl-ACP synthetase and superoxide dismutase into the subject under conditions such that the nucleic acid expresses the soluble triacylglycerol biosynthetic enzymes individually or in combination, so as to thereby treat the subject.

Summary of Invention Paragraph - BSTX (45):
[0041] This invention provides a transgenic, nonhuman mammal comprising the isolated nucleic acid, which encode lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein (ACP), acyl-ACP synthetase and superoxide dismutase.

Summary of Invention Paragraph - BSTX (47):
[0043] This invention provides antibodies directed to an epitope of a purified lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein, acyl-ACP synthetase and superoxide dismutase. This invention provide antibodies capable of specifically binding to a purified lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein, acyl-ACP synthetase and superoxide dismutase.

Summary of Invention Paragraph - BSTX (49):
[0045] This invention provides a purified lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein, acyl-ACP synthetase and superoxide dismutase related gene products.

Summary of Invention Paragraph - BSTX (50):
[0046] This invention provides an oligonucleotide of at least 15 nucleotides capable of specifically hybridizing with a unique sequence of nucleotides present within a nucleic acid which encode lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein (ACP), acyl-ACP synthetase and superoxide dismutase related gene products lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein (ACP), acyl-ACP synthetase and superoxide dismutase.

Summary of Invention Paragraph - BSTX (51):
[0047] This invention provides a nucleic acid having a sequence complementary to the sequence of the isolated nucleic acid which encode lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein (ACP), acyl-ACP synthetase and superoxide dismutase related gene products.

Summary of Invention Paragraph - BSTX (52):
[0048] This invention provides antibodies directed to epitopes of a purified components of TBC lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase, diacylglycerol acyltransferase, acyl carrier protein (ACP),

acyl-ACP synthetase and superoxide dismutase related gene products. This invention provides antibodies capable of specifically binding to a purified TBC and its components related gene products.

Claims Text - CLTX (7):
7. Novel soluble TAG biosynthetic enzymes in yeast as in claim 1, where in lysophosphatidic acid acyltransferase is identified by immunological cross reactivity to the peptide sequence ALELQADDFNK (as in peptide SEQ ID 2), diacylglycerol acyltransferase is identified by immunological cross reactivity to the peptide **sequence XLWAVVGAQPFGGARGS (as in peptide SEQ ID 7) and phosphatidic acid phosphatase** is identified by immunological cross reactivity to peptides NALTGLHMGGGK (as in peptide SEQ ID 4) and YVEGARP (as in peptide SEQ ID 6).

Claims Text - CLTX (25):
25. A method for treating a subject who has an imbalance in triglyceride (triacylglycerol) levels due to a defect in the synthesis of soluble triglyceride, which comprises introducing the **isolated nucleic acid which encodes lysophosphatidic acid acyltransferase, phosphatidic acid phosphatase,** diacylglycerol acyltransferase, acyl carrier protein (ACP), and acyl-ACP synthetase into the subject under conditions such that the nucleic acid expresses the soluble triacylglycerol biosynthetic enzymes individually or in combination, so as to thereby treat the subject.

PGPUB-DOCUMENT-NUMBER: 20020102604

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020102604 A1

TITLE: Full-length human cDNAs encoding potentially secreted proteins

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

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Milne Edwards, Jean-Baptiste	Paris		FR	
Dumas	Petit Lancy		CH	
Bougueleret, Lydie	Paris		FR	
Jobert, Severin				

APPL-NO: 09/ 731872

DATE FILED: December 7, 2000

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60169629 19991208 US

non-provisional-of-provisional 60187470 20000306 US

US-CL-CURRENT: 435/7.1, 530/350 , 536/23.1

ABSTRACT:

The invention concerns GENSET polynucleotides and polypeptides. Such GENSET products may be used as reagents in forensic analyses, as chromosome markers, as tissue/cell/organelle-specific markers, in the production of expression vectors. In addition, they may be used in screening and diagnosis assays for abnormal GENSET expression and/or biological activity and for screening compounds that may be used in the treatment of GENSET-related disorders.

RELATED APPLICATION

[0001] The present application claims priority, under 35 USC .sctn. 19(e), to the U.S. Provisional Patent Applications Serial Nos. 60/169,629 and 60/187,470 filed Dec. 8, 1999, and Mar. 6, 2000, respectively, the disclosures of which are incorporated herein by reference in their entireties.

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Detail Description Paragraph - DETX (1378):

[1454] The protein of SEQ ID NO:399 is encoded by a cDNA that has homology to many forms of alternative splicing of PAP2 genes. For example, the protein of SEQ ID NO:399 has 29% homology with human phosphatidic acid phosphohydrolase type-2C protein. The protein of SEQ ID NO:399 also has 40% homology with human phosphatidic acid phosphatase 2B protein. In addition, the protein of SEQ ID NO:399 has 33% homology with human type 2 phosphatidic acid phosphatase alpha-2 protein. PAP2-alpha2 is one of the two isoforms with PAP2-alphal, presumed to be alternative splice variants from a single gene.

Detail Description Paragraph - DETX (1379):

[1455] Northern analysis has shown that PAP2-alpha mRNA expression was suppressed in several tumor tissues, indicating that PAP-2 may act as a tumor suppressor. The relationship of PAP and tumor suppression is further evidenced in findings that PAP activity is lower in fibroblast cell lines transformed with either the ras orfps oncogene than in the parental ratl cell line (Brindley et al; Chem. Phys. Lipids 80: 45-57; 1996, the disclosure of which is incorporated herein by reference in its entirety). As discussed above, a decrease in PAP activity in transformed cells correlates with a concomitant increase in PA concentration. Moreover, elevated PAP activity and lower levels of PA have been observed in contact-inhibited fibroblasts relative to proliferating and transformed fibroblasts (Brindley et al ; Chem. Phys. Lipids 80: 45-57; 1996, the disclosure of which is incorporated herein by reference in its entirety). Therefore, the protein of SEQ ID NO:399 or fragments thereof may be used to decrease cell division and as such can provide a useful tool in treating cancer. Subsequent analysis of colon tumor tissue derived from four donors confirmed lower expression of PAP2-alpha than in matching normal colon tissue. Considering these data and previous demonstrations that certain transformed cell lines have lower PAP activity, human PAP cDNAs may be used for gene therapy for certain tumors (Leung D. W., Tompkins C. K., White T.; DNA Cell Biol.17 : 377-385 (1998), the disclosure of which is incorporated herein by reference in its entirety). Accordingly, one embodiment of the present invention is the use of the protein of SEQ ID NO: 399 or a fragment thereof as a tumor suppressor. For example, a nucleic acid expressing the protein of SEQ ID NO:399 or a fragment thereof may be introduced into an individual suffering from cancer in order to ameliorate or eliminate the cancer. In fact, nucleic acids encoding human phosphatidic acid phosphatases have been used to regulate levels of lipid cellular mediators and in gene therapy of e.g. cancer (PCT publication WO98/46730, the disclosure of which is incorporated herein by reference in its entirety).

Detail Description Paragraph - DETX (1380):

[1456] In another embodiment of the present invention, the protein of SEQ ID NO:399 or a fragment thereof can be used to control the balance of lipid mediators of cellular activation and signal transduction. The protein of the invention has 33% homology with human phosphatidic acid phosphatase 2A protein. PAP2A is an integral membrane glycoprotein at the cell surface that plays an active role in the hydrolysis and uptake of lipids from the extracellular space (Roberts R Z, Morris A J; Biochim Biophys Acta 2000 Aug 24;1487(l):33-49, the disclosure of which is incorporated herein by reference in its entirety). Accordingly, the level or activity of the protein of SEQ ID NO:399 may be modulated to influence the rate or extent of hydrolysis and uptake of lipids from the extracellular space using methods such as those described herein.

US-PAT-NO: 6875781

DOCUMENT-IDENTIFIER: US 6875781 B2

TITLE: Pyridines and uses thereof

DATE-ISSUED: April 5, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hong; Feng	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon	WA	N/A	N/A

APPL-NO: 10/ 667916

DATE FILED: September 22, 2003

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/460,782, filed Apr. 4, 2003, which application is incorporated by reference herein in its entirety.

US-CL-CURRENT: 514/352, 514/345 , 546/290 , 546/304 , 546/312

ABSTRACT:

The invention relates to pyridines and uses thereof, including to inhibit lysophosphatidic acid acyltransferase .beta. (LPAAT-.beta.) activity and/or proliferation of cells such as tumor cells.

25 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Other Reference Publication - OREF (11):
Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," Journal of Biological Chemistry 266(31): 20732-20743, Nov. 5, 1991.

Other Reference Publication - OREF (23):
Leung et al., "Molecular Cloning of Two Alternatively Spliced Forms of Human Phosphatidic Acid Phosphatase cDNAs that Are Differentially Expressed in Normal and Tumor Cells," DNA and Cell Biology 17(4): 377-385, Apr. 1998.

US-PAT-NO: 6693105

DOCUMENT-IDENTIFIER: US 6693105 B1

TITLE: Hydroxyl-containing compounds

DATE-ISSUED: February 17, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Porubek; David	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon	WA	N/A	N/A
Woodson; Paul	Edmonds	WA	N/A	N/A
Klaus; Stephen J.	Seattle	WA	N/A	N/A
Kumar; Anil M.	Mercer Island	WA	N/A	N/A
Tulinsky; John	Seattle	WA	N/A	N/A

APPL-NO: 09/ 361145

DATE FILED: July 27, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 08/756,703, filed Nov. 26, 1996 now U.S. Pat. No. 6,133,274, and U.S. application Ser. No. 09/288,556, filed Apr. 9, 1999. U.S. application Ser. No. 08/756,703 is a continuation of U.S. application Ser. No. 08/153,356, filed Nov. 16, 1993, which is a continuation-in-part of U.S. application Ser. No. 07/976,353, filed Nov. 16, 1992, now U.S. Pat. No. 5,473,070. U.S. application Ser. No. 09/288,556 is a continuation-in-part of U.S. application Ser. No. 09/008,020, which was filed Jan. 16, 1998. The disclosures of the aforementioned applications are incorporated by reference herein in their entirety.

US-CL-CURRENT: 514/263.3, 436/98 , 514/263.2 , 544/267

ABSTRACT:

Disclosed are therapeutic compounds having the formula:

(R).sub.j --(CORE MOIETY),

including resolved enantiomers, diastereomers, hydrates, salts, solvates or mixtures thereof where j is an integer from one to three. The core moiety is a bicyclic ring structure having at least one heterocyclic ring that contains five to six ring atoms and up to two nitrogen heteroatoms. R is selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, C.sub.1-6 alkyl or C.sub.1-6 alkenyl, and at least one R has the formula I: ##STR1##

n is an integer from 1 to 20, at least one of X or Y is --OH. Another of X or Y, which is not --OH, is hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 --or (CH.sub.3).sub.2 --CH.sub.2 --, and each W.sub.1, W.sub.2, and W.sub.3 is independently hydrogen, CH.sub.3 --, CH.sub.3

--CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --. The X, Y, W.sub.1, W.sub.2, or W.sub.3 alkyl groups may be unsubstituted or substituted by an hydroxyl, halo or dimethylamino group. The disclosed compounds and therapeutic compositions thereof are useful in treating individuals having a disease or treatment-induced toxicity, mediated by second messenger activity.

18 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

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Detailed Description Text - DETX (26):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 6610835

DOCUMENT-IDENTIFIER: US 6610835 B1

TITLE: Sphingolipid derivatives and their methods of use

DATE-ISSUED: August 26, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liotta; Dennis C.	McDonough	GA	N/A	N/A
Merrill, Jr.; Alfred H.	Stone Mountain	GA	N/A	N/A
Keane; Thomas E.	Dunwoody	GA	N/A	N/A
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APPL-NO: 09/ 249211

DATE FILED: February 12, 1999

PARENT-CASE:

This application claims priority to U.S. provisional application No. 60/074,536, filed on Feb. 12, 1998.

US-CL-CURRENT: 536/4.1, 536/17.2 , 536/17.9 , 536/18.2

ABSTRACT:

Derivatives of sphingolipids of the formula: ##STR1##

are provided wherein the substituents are as defined in the specification and wherein there is at least one R.sup.2 substituent in the sphingolipid derivative. The compounds are useful in the treatment of of abnormal cell proliferation, including benign and malignant tumors, the promotion of cell differentiation, the induction of apoptosis, the inhibition of protein kinase C, and the treatment of inflammatory conditions, psoriasis, inflammatory bowel disease as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissue. The invention also includes a method for triggering the release of cytochrome c from mitochondria that includes administering an effective amount of a sphingolipid or its derivative or prodrug to a host in need thereof. Further, the invention provides a method for treating bacterial infections, including those that influence colon cancer and other disorders of the intestine, that includes administering an effective amount of one of the active compounds identified herein.

42 Claims, 18 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 16

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Brief Summary Text - BSTX (6):
The hydroxyl groups at positions 1, 3 and sometimes 4 or 6 are also relevant

to the behavior of these compounds. This has mostly been considered from the perspective of how hydrogen bonding in the interfacial region of the bilayer affects membrane structure (Thompson and Tillack, Annu. Biophys. Chem., 14:361-386, 1985). However, in a study of **phosphatidic acid phosphatase purified** from yeast (Wu et al., J. Biol. Chem. 268:13830-13837, 1993), inhibition of this enzyme by long-chain bases showed a considerable preference for phytosphingosine and sphinganine over sphingosine, which matches the types of sphingoid bases found in yeast. Therefore, these functional groups appear to be present both for structural purposes and to allow optimum interaction with cellular targets.

US-PAT-NO: 6558914

DOCUMENT-IDENTIFIER: US 6558914 B1

TITLE: Human lysophosphatidic acid acyltransferase

DATE-ISSUED: May 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hillman; Jennifer L.	Mountain View	CA	N/A	N/A
Yue; Henry	Sunnyvale	CA	N/A	N/A
Guegler; Karl J.	Menlo Park	CA	N/A	N/A
Corley; Neil C.	Mountain View	CA	N/A	N/A

APPL-NO: 09/ 388995

DATE FILED: September 2, 1999

PARENT-CASE:

This application is a divisional application of U.S. application Ser. No. 09/259,206, filed Mar. 1, 1999, issued Dec. 14, 1999 as U.S. Pat. No. 6,001,620 which is a divisional of U.S. application Ser. No. 09/030,652, filed Feb. 25, 1998, issued Mar. 30, 1999, as U.S. Pat. No. 5,888,793.

US-CL-CURRENT: 435/15, 435/193

ABSTRACT:

The invention provides a human lysophosphatidic acid acyltranferase (HLPAAT) and polynucleotides which identify and encode HLPAAT. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for treating or preventing disorders associated with expression of HLPAAT.

7 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

---------- KWIC --------

Other Reference Publication - OREF (3):
Bursten, S.L. et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells", J. Biol. Chem., 266(31): 20732-20743 Nov. 5, 1991.

US-PAT-NO: 6495739

DOCUMENT-IDENTIFIER: US 6495739 B1

TITLE: Plant phosphatidic acid phosphatases

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lassner; Michael W.	Davis	CA	N/A	N/A
Ruezinsky; Diane M.	Woodland	CA	N/A	N/A

APPL-NO: 09/ 360376

DATE FILED: July 23, 1999

PARENT-CASE:

This application is a continuation-in-part of application Ser. No. 09/122,315 filed Jul. 24, 1998.

US-CL-CURRENT: 800/281, 435/419 , 435/468 , 536/23.6 , 800/298

ABSTRACT:

By this invention, novel nucleic acid sequences encoding for phosphatidic acid phosphatase (PAP) proteins are provided, wherein PAP protein is active in the formation of diacylglycerol from phosphatidic acid. Also considered are amino acid and nucleic acid sequences obtainable from PAP nucleic acid sequences and the use of such sequences to provide transgenic host cells capable of producing altered lipid compositions and total lipid levels.

74 Claims, 18 Drawing figures

Exemplary Claim Number: 9

Number of Drawing Sheets: 18

---------- KWIC ---------

Abstract Text - ABTX (1):

By this invention, novel nucleic acid sequences encoding for phosphatidic acid phosphatase (PAP) proteins are provided, wherein PAP protein is active in the formation of diacylglycerol from phosphatidic acid. Also considered are amino acid and nucleic acid sequences obtainable from PAP nucleic acid sequences and the use of such sequences to provide transgenic host cells capable of producing altered lipid compositions and total lipid levels.

Detailed Description Text - DETX (2):

In accordance with the subject invention, nucleotide sequences are provided which are capable of coding sequences of amino acids, such as, a protein, polypeptide or peptide, which encode phosphatidic acid phosphatase (also referred to herein as PAP). The novel nucleic acid sequences find use in the preparation of constructs to direct their expression in a host cell. Furthermore, the novel nucleic acid sequences find use in the preparation of

plant expression constructs to modify the fatty acid composition as well as the fatty acid content of a host plant cell.

Detailed Description Text - DETX (3):
In one embodiment of the present invention, nucleic acid sequences are provided which encode for plant phosphatidic acid phosphatase. An Arabidopsis thaliana PAP nucleic acid sequence is identified from databases using oligonucleotide sequences derived from conserved sequences of mouse, rat, human, and yeast phosphatidic acid phosphatase amino acid sequences. The Arabidopsis PAP nucleic acid sequence is used to transform yeast, E. coli and plants (Arabidopsis and Brassica napus) to confirm the identity of the clone.

Detailed Description Text - DETX (4):
In order to identify plant phosphatidic acid phosphatase related nucleic acid and amino acid sequences, a known PAP nucleic acid sequence from a mammalian source was used to identify additional PAP nucleic acid sequences from other mammalian and yeast sources. As described in more detail in the following examples, the nucleic acid and amino acid sequence of a mouse plasmalemma form of PAP is used to identify related DNA and protein sequences from public databases. The protein sequences of the PAP related amino acid sequences are compared using protein alignment software applications known in the art. Two amino acid sequences, TDIAKXXIGRLRPHFLXXC (SEQ ID NO:1) and LSRVSDYKHHWSDV (SEQ ID NO:2), are identified which are highly conserved between the different sequences.

Detailed Description Text - DETX (10):
In another embodiment of the present invention, methods for isolating additional sequences encoding phosphatidic acid phosphatase from other plant species are provided. Such PAP enzymes may find use in producing transgenic plants capable to accumulate high levels of unique oil compositions. For example, identification of a PAP from Cuphea species may have preferential activity for medium-chain phosphatidic acid species. By medium-chain preferring phosphatidic acid species is meant that the enzyme encoded by the PAP nucleic acid sequence demonstrates a preference for dephosphorylating phosphatidic acid species containing C6, C8, C10, C12 and/or C14 fatty acyl groups at the sn-1 and/or sn-2 positions over PA species containing different fatty acyl groups in the sn-1 and/or sn-2 positions.

Detailed Description Text - DETX (20):
In addition, not only can sequences provided herein be used to identify homologous phosphatidic acid phosphatases, but the resulting sequences obtained therefrom may also provide a further method to obtain plant phosphatidic acid phosphatases from other plant sources. In particular, PCR may be a useful technique to obtain related plant PAP from sequence data provided herein. One skilled in the art will be able to design oligonucleotide probes based upon sequence comparisons or regions of typically highly conserved sequence.

Detailed Description Text - DETX (22):
Nucleic acids (genomic DNA, plasmid DNA, cDNA, synthetic DNA, mRNA, etc.) encoding phosphatidic acid phosphatase or amino acid sequences of the purified enzymes, which permit design of nucleic acid probes facilitating the isolation of DNA coding sequences therefor, are known in the art and are available for use in the methods of the present invention. It is generally recognized to an artisan skilled in the field to which the present invention pertains that the nucleic acid sequences provided herein and the amino acid sequences derived therefrom may be used to isolate other potential PAP genes from GenBank using DNA and peptide search techniques generally known in the art.

Detailed Description Text - DETX (24):

The nucleic acid sequences which encode plant phosphatidic acid phosphatases may be used in various constructs, for example, as probes to obtain further sequences. Alternatively, these sequences may be used in conjunction with appropriate regulatory sequences to increase levels of the respective PAP of interest in a host cell for recovery or study of the enzyme in vitro or in vivo or to decrease levels of the respective PAP of interest for some applications when the host cell is a plant entity, including plant cells, plant parts (including but not limited to seeds, cuttings or tissues) and plants.

Detailed Description Text - DETX (57):
The gene encoding a mouse plasmalemma form of phosphatidic acid phosphatase has been previously cloned and sequenced (Kai, et al. (1996), J. Biol. Chem., 271:18931-18938). The protein sequence w as obtained from Genbank and used to search p rotei n and DNA databases to identify related sequences. Sequences from rat, human, C. elegans and yeast were identified as being related to the mouse PAP sequence. The sequences of PAP from mouse, rat, human and yeast were aligned (FIG. 1) using MacVector (Oxford Molecular, Inc.), and two conserved peptide sequences were identified; TDIAKXXIGRLRPHFLXXC (SEQ ID NO:1) and LSRVSDYKHHWSDV (SEQ ID NO: 2). These two protein sequences were used to search the Arabidopsis EST database, and one cDNA clone, 158J20XP, was identified as containing an amino acid sequence motif 71% similar to the LSRVSDYKHHWSDV motif (SEQ ID NO: 2).

Claims Text - CLTX (1):
1. An isolated DNA sequence encoding a plant phosphatidic acid phosphatase protein, wherein said plant phosphatidic acid phosphatase protein encoded by said nucleic acid molecule includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2.

Claims Text - CLTX (2):
2. The DNA sequence of claim 1, wherein said phosphatidic acid phosphatase protein is found in soybean.

Claims Text - CLTX (3):
3. The DNA sequence of claim 2, wherein said phosphatidic acid phosphatase protein comprises an amino acid sequence of SEQ ID NO: 16.

Claims Text - CLTX (4):
4. The DNA sequence of claim 2, wherein said phosphatidic acid phosphatase protein comprises an amino acid sequence of SEQ ID NO: 17.

Claims Text - CLTX (6):
6. A recombinant DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2.

Claims Text - CLTX (7):
7. A plant cell comprising a heterologous DNA construct that comprises, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2.

Claims Text - CLTX (8):
8. A plant comprising a cell that comprises a DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2.

Claims Text - CLTX (9):
9. A method of modifying the lipid composition in a plant cell, said method comprising: transforming a plant cell with DNA comprising as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence, capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2, and growing said plant cell under conditions where transcription of said plant phosphatidic acid phosphatase is initiated, whereby said lipid composition is modified.

Claims Text - CLTX (10):
10. A method according to claim 9, wherein said encoding sequence comprises at least a portion of a plant phosphatidic acid phosphatase in an antisense orientation, whereby the transcribed mRNA from said encoding sequence is complementary to the equivalent mRNA transcribed from the endogenous gene, whereby the activity of said phosphatidic acid phosphatase protein in said plant cell is suppressed.

Claims Text - CLTX (12):
12. A method according to claim 9, wherein said phosphatidic acid phosphatase protein encoding sequence is in a sense orientation.

Claims Text - CLTX (14):
14. A method of modifying the lipid composition in a plant cell, said method comprising: transforming a plant cell with DNA comprising as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, and growing said plant cell under conditions where transcription of said soybean phosphatidic acid phosphatase is initiated and where said lipid composition is modified.

Claims Text - CLTX (15):
15. The method according to claim 14, wherein said soybean phosphatidic acid phosphatase is encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs: 10 and 11.

Claims Text - CLTX (16):
16. The method according to claim 14, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 17.

Claims Text - CLTX (20):
20. A method of modifying the lipid composition in a plant cell comprising: transforming a plant cell with DNA comprising as operably linked in the 5' to 3' direction of transcription, a promoter functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a

plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2, and growing said plant cell under conditions where transcription of said plant phosphatidic acid phosphatase is initiated and where said lipid composition is modified.

Claims Text - CLTX (24):
24. A method of modifying the lipid composition in a plant cell comprising: transforming a plant cell with DNA comprising as operably linked in the 5' to 3' direction of transcription, a promoter functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, and growing said plant cell under conditions where transcription of said soybean phosphatidic acid phosphatase is initiated and where said lipid composition is modified.

Claims Text - CLTX (25):
25. The method according to claim 24, wherein said soybean phosphatidic acid phosphatase is encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs: 10 and 11.

Claims Text - CLTX (26):
26. The method according to claim 24, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 17.

Claims Text - CLTX (30):
30. A recombinant DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said soybean phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2.

Claims Text - CLTX (31):
31. The recombinant DNA construct according to claim 30, wherein said soybean phosphatidic acid phosphatase is encoded by a sequence selected from the group consisting of SEQ ID NOs: 10 and 11.

Claims Text - CLTX (32):
32. The recombinant DNA construct according to claim 30, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 17.

Claims Text - CLTX (36):
36. A recombinant DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a promoter functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said soybean phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2.

Claims Text - CLTX (37):
37. The recombinant DNA construct according to claim 36, wherein said soybean phosphatidic acid phosphatase is encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs: 10 and 11.

Claims Text - CLTX (38):
38. The recombinant DNA construct according to claim 36, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 17.

Claims Text - CLTX (42):
42. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a heterologous transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2, and expressing said plant phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (47):
47. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a heterologous transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, and expressing said soybean phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (52):
52. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a heterologous DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2, and expressing said plant phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (54):
54. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a heterologous DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, and expressing said soybean phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (56):
56. The method according to claim 54, wherein said soybean phosphatidic acid phosphatase is encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs: 10 and 11.

Claims Text - CLTX (57):
57. The method according to claim 54, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 17.

Claims Text - CLTX (58):
58. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a heterologous promoter functional in a plant cell, a DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2, and expressing said plant phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (63):
63. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a heterologous promoter functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, and expressing said soybean phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (68):
68. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a promoter functional in a plant cell, a heterologous DNA structural gene sequence encoding a plant phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, wherein said phosphatidic acid phosphatase encoded by said DNA structural gene includes an amino acid fragment having at least 70% sequence identity to SEQ ID NO: 2, and expressing said plant phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (70):
70. A method of increasing fatty acid level in a plant cell comprising: growing a plant containing said plant cell, wherein said plant cell comprises a DNA construct that comprises as operably linked in the 5' to 3' direction of transcription, a promoter functional in a plant cell, a heterologous DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in a plant cell, and expressing said soybean phosphatidic acid phosphatase, wherein said fatty acid level is increased.

Claims Text - CLTX (72):
72. The method according to claim 70, wherein said soybean phosphatidic acid phosphatase is encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs: 10 and 11.

Claims Text - CLTX (73):
73. The method according to claim 70, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 17.

Claims Text - CLTX (74):
74. An isolated DNA sequence encoding a soybean phosphatidic acid phosphatase, wherein said soybean phosphatidic acid phosphatase comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 16 and 17.

Other Reference Publication - OREF (11):
Kai, et al., "Cloning and Characterization of Two human Isozymes of Mg2+-independent Phosphatidic Acid Phosphatase", The Journal of Biological Chemistry (1997) vol. 272, No. 39 pp: 24572-24578.

US-PAT-NO: 6476294

DOCUMENT-IDENTIFIER: US 6476294 B1
See image for Certificate of Correction

TITLE: Plant phosphatidic acid phosphatases

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lassner; Michael W.	Davis	CA	N/A	N/A
Ruezinsky; Diane M.	Woodland	CA	N/A	N/A

APPL-NO: 09/ 122315

DATE FILED: July 24, 1998

US-CL-CURRENT: 800/281, 435/419 , 435/468 , 536/23.6 , 800/298

ABSTRACT:

By this invention, novel nucleic acid sequences encoding for phosphatidic acid phosphatase (PAP) proteins are provided, wherein said PAP protein is active in the formation of diacylglycerol from phosphatidic acid. Also considered are amino acid and nucleic acid sequences obtainable from PAP nucleic acid sequences and the use of such sequences to provide transgenic host cells capable of producing altered lipid compositions and total lipid levels.

24 Claims, 10 Drawing figures

Exemplary Claim Number: 14

Number of Drawing Sheets: 10

---------- KWIC ---------

Abstract Text - ABTX (1):
By this invention, novel nucleic acid sequences encoding for phosphatidic acid phosphatase (PAP) proteins are provided, wherein said PAP protein is active in the formation of diacylglycerol from phosphatidic acid. Also considered are amino acid and nucleic acid sequences obtainable from PAP nucleic acid sequences and the use of such sequences to provide transgenic host cells capable of producing altered lipid compositions and total lipid levels.

Brief Summary Text - BSTX (15):
Stymne, et al., (1987), The Biochemistry of Plants, 9:192-193 describes phosphatidic acid phosphatase as a rate limiting step in the production of triacylglycerol in plants. Brindley, (1978), Int. J. Obes. 2:7-16 describes the rate limiting step of triacylglycerol biosynthesis in animals as the dephosphorylation of phosphatidic acid. Kai, et al. (1996), J. Biol. Chem., 271:18931-18938, describes the cloning of a gene encoding a mouse plasmalemma form of phosphatidic acid phosphatase. Berg, et al. (1997) Biochemica et Biophysica Acta, 1330:225-232 describes the purification of a phosphatase which hydrolyzes phosphatidic acid from Acholeplasma laidlawii. Carman (1997) Biochemica et Biophysica Acta 1348:45-55 describes phosphatidate phosphatases

in Saccharomyces cerevisiae and Escherichia coli.

Detailed Description Text - DETX (3):
In one embodiment of the present invention, nucleic acid sequences are provided which encode for plant phosphatidic acid phosphatase. An Arabidopsis thaliana PAP nucleic acid sequence is identified from databases using oligonucleotide sequences derived from conserved sequences of mouse, rat, human, and yeast phosphatidic acid phosphatase amino acid sequences. The Arabidopsis PAP nucleic acid sequence is used to transform yeast, E. coli and plants (Arabidopsis and Brassica napus) to confirm the identity of the clone.

Detailed Description Text - DETX (4):
In order to identify plant phosphatidic acid phosphatase related nucleic acid and amino acid sequences, a known PAP nucleic acid sequence from a mammalian source was used to identify additional PAP nucleic acid sequences from other mammalian and yeast sources. As described in more detail in the following examples, the nucleic acid and amino acid sequence of a mouse plasmalemma form of PAP is used to identify related DNA and protein sequences from public databases. The protein sequences of the PAP related amino acid sequences are compared using protein alignment software applications known in the art. Two amino acid sequences, TDIAKXXIGRLRPHFLXXC (SEQ ID NO:13) and LSRVSDYKHHWSDV (SEQ ID NO:14), are identified which are highly conserved between the different sequences.

Detailed Description Text - DETX (10):
In another embodiment of the present invention, methods for isolating additional sequences encoding phosphatidic acid phosphatase from other plant species are provided. Such PAP enzymes may find use in producing transgenic plants capable to accumulate high levels of unique oil compositions. For example, identification of a PAP from Cuphea species may have preferential activity for medium-chain phosphatidic acid species. By medium-chain preferring phosphatidic acid species is meant that the enzyme encoded by the PAP nucleic acid sequence demonstrates a preference for dephosphorylating phosphatidic acid species containing C6, C8, C10, C12 and/or C14 fatty acyl groups at the sn-1 and/or sn-2 positions over PA species containing different fatty acyl groups in the sn-1 and/or sn-2 positions.

Detailed Description Text - DETX (20):
In addition, not only can sequences provided herein be used to identify homologous phosphatidic acid phosphatases, but the resulting sequences obtained therefrom may also provide a further method to obtain plant phosphatidic acid phosphatases from other plant sources. In particular, PCR may be a useful technique to obtain related plant PAP from sequence data provided herein. One skilled in the art will be able to design oligonucleotide probes based upon sequence comparisons or regions of typically highly conserved sequence.

Detailed Description Text - DETX (22):
Nucleic acids (genomic DNA, plasmid DNA, cDNA, synthetic DNA, mRNA, etc.) encoding phosphatidic acid phosphatase or amino acid sequences of the purified enzymes, which permit design of nucleic acid probes facilitating the isolation of DNA coding sequences therefor, are known in the art and are available for use in the methods of the present invention. It is generally recognized to an artisan skilled in the field to which the present invention pertains that the nucleic acid sequences provided herein and the amino acid sequences derived therefrom may be used to isolate other potential PAP genes from GenBank using DNA and peptide search techniques generally known in the art.

Detailed Description Text - DETX (24):
The nucleic acid sequences which encode plant phosphatidic acid phosphatases

may be used in various constructs, for example, as probes to obtain further sequences. Alternatively, these sequences may be used in conjunction with appropriate regulatory sequences to increase levels of the respective PAP of interest in a host cell for recovery or study of the enzyme in vitro or in vivo or to decrease levels of the respective PAP of interest for some applications when the host cell is a plant entity, including plant cells, plant parts (including but not limited to seeds, cuttings or tissues) and plants.

Detailed Description Text - DETX (57):
The gene encoding a mouse plasmalemma form of phosphatidic acid phosphatase has been previously cloned and sequenced (Kai, et al. (1996), J. Biol. Chem., 271:18931-18938). The protein sequence was obtained from Genbank and used to search protein and DNA databases to identify related sequences. Sequences from rat, human, C. elegans and yeast were identified as being related to the mouse PAP sequence. The sequences of PAP from mouse (SEQ ID NO: 2), rat (SEQ ID NO: 3), human (SEQ ID NO: 1) and yeast (SEQ ID NO: 4) were aligned (FIG. 1) using Macvector (Oxford Molecular, Inc.), and two conserved peptide sequences were identified; TDIAKXXIGRLRPHFLXXC (SEQ ID NO:13) and LSRVSDYKHHWSDV (SEQ ID NO:14). These two protein sequences were used to search the Arabidopsis EST database, and one cDNA clone, 158J20XP, was identified as containing an amino acid sequence motif 71% similar to the LSRVSDYKHHWSDV (SEQ ID NO:14) motif.

Claims Text - CLTX (1):
1. An isolated DNA sequence encoding a plant phosphatidic acid phosphatase protein, wherein said plant phosphatidic acid phosphatase protein is from Arabidopsis thaliana.

Claims Text - CLTX (2):
2. The isolated DNA sequence of claim 1, wherein said plant phosphatidic acid phosphatase protein is encoded by the sequence of SEQ ID NO: 5.

Claims Text - CLTX (3):
3. The isolated DNA sequence of claim 1, wherein said plant phosphatidic acid phosphatase protein is encoded by the sequence of SEQ ID NO: 6.

Claims Text - CLTX (4):
4. The isolated DNA sequence of claim 1, wherein said plant phosphatidic acid phosphatase protein is encoded by the sequence of SEQ ID NO: 7.

Claims Text - CLTX (5):
5. An isolated DNA sequence encoding a plant phosphatidic acid phosphatase protein, wherein said plant phosphatidic acid phosphatase protein is from corn.

Claims Text - CLTX (7):
7. An isolated DNA sequence encoding a plant phosphatidic acid phosphatase protein, wherein said plant phosphatidic acid phosphatase protein is from soybean.

Claims Text - CLTX (8):
8. The isolated DNA sequence of claim 2, wherein said plant phosphatidic acid phosphatase protein is encoded by the sequence of SEQ ID NO: 10.

Claims Text - CLTX (9):
9. The isolated DNA sequence of claim 3, wherein said plant phosphatidic acid phosphatase protein is encoded by the sequence of SEQ ID NO:11.

Claims Text - CLTX (11):
11. A recombinant DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional

in a plant cell, a DNA structural gene sequence encoding an Arabidopsis thaliana phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (12):
12. A plant cell having a DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding an Arabidopsis thaliana phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (13):
13. A plant having a plant cell comprising a DNA construct that comprises, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding an Arabidopsis thaliana phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (14):
14. A method of modifying the lipid composition in a plant cell, said method comprising: transforming a plant cell with DNA comprising as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region fictional in a plant cell, a DNA structural gene sequence encoding an Arabidopsis thaliana phosphatidic acid phosphatase, and a transcription termination sequence, capable of terminating transcription in said plant cell, and growing said plant cell under conditions wherein transcription of said Arabidopsis thaliana phosphatidic acid phosphatase is initiated, whereby said lipid composition is modified.

Claims Text - CLTX (15):
15. A method according to claim 14, wherein said encoding sequence comprises at least a portion of an Arabidopsis thaliana phosphatidic acid phosphatase in an antisense orientation, whereby the transcribed mRNA from said encoding sequence is complementary to the equivalent mRNA transcribed from the endogenous gene, whereby the activity of said Arabidiopsis thaliana phosphatidic acid phosphatase protein in said plant cell is suppressed.

Claims Text - CLTX (17):
17. A method according to claim 14, wherein said Arabidopsis thaliana phosphatidic acid phosphatase protein encoding sequence is in a sense orientation.

Claims Text - CLTX (19):
19. A recombinant DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a corn phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (20):
20. A recombinant DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in a plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (21):
21. A plant cell having a DNA construct comprising, as operably linked in

the 5' to 3' direction of transcription, a transcriptional initiation region functional in said plant cell, a DNA structural gene sequence encoding a corn phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (22):
22. A plant cell having a DNA construct comprising, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in said plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (23):
23. A plant having a plant cell comprising a DNA construct that comprises, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in said plant cell, a DNA structural gene sequence encoding a corn phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Claims Text - CLTX (24):
24. A plant having a plant cell comprising a DNA construct that comprises, as operably linked in the 5' to 3' direction of transcription, a transcriptional initiation region functional in said plant cell, a DNA structural gene sequence encoding a soybean phosphatidic acid phosphatase, and a transcription termination sequence capable of terminating transcription in said plant cell.

Other Reference Publication - OREF (4):
Kai, et al., "Cloning and Characterization of Two human Isozymes of Mg2+-independent Phosphatidic Acid Phosphatase", The Journal of Biological Chemistry (1997) vol. 272, No. 39 pp: 24572-24578.

US-PAT-NO: 6331254

DOCUMENT-IDENTIFIER: US 6331254 B1

TITLE: Methods of separation and detection

DATE-ISSUED: December 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
White; Thayer	Clyde Hill	WA	N/A	N/A
Nudelman; Edward	Seattle	WA	N/A	N/A

APPL-NO: 09/ 465678

DATE FILED: December 17, 1999

PARENT-CASE:

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Ser. No. 09/049,941, filed Mar. 30, 1998, now abandoned and a continuation of PCT/US99/06803 filed Mar. 30, 1999.

US-CL-CURRENT: 210/658, 210/198.3 , 436/162 , 436/172

ABSTRACT:

Methods which employ thin layer chromatography for separating and detecting hydrophobic target molecules are particularly useful in separating biologically relevant lipids. By utilizing non-destructive detection techniques, these methods also can be adapted to further quantification or structural analysis.

18 Claims, 7 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

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Other Reference Publication - OREF (14):
Bursten et al.; "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells"; J. Biol. Chem., 1991; vol. 266, No. 31; pp. 20732-20743.

US-PAT-NO: 6242179

DOCUMENT-IDENTIFIER: US 6242179 B1

TITLE: Human phosphatases

DATE-ISSUED: June 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shah; Purvi	Sunnyvale	CA	N/A	N/A
Hillman; Jennifer L.	Mountain View	CA	N/A	N/A
Corley; Neil C.	Mountain View	CA	N/A	N/A
Lal; Preeti	Santa Clara	CA	N/A	N/A

APPL-NO: 08/ 992035

DATE FILED: December 17, 1997

US-CL-CURRENT: 435/6, 435/196 , 435/252.3 , 435/320.1 , 435/325 , 435/69.1 , 536/23.1 , 536/23.2 , 536/23.5

ABSTRACT:

The invention provides human phosphatases (HPA) and polynucleotides which identify and encode HPA. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for treating disorders associated with expression of HPA.

10 Claims, 17 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 17

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Other Reference Publication - OREF (5):
Kai KM, et al.: "Cloning and characterization of two human isozymes of Mg2+independent phosphatidic acid phosphatases" Journal of Biological Chemistry, vol. 272, No. 39, Sep. 26, 1997 (Sep. 26, 1997), pp. 24572-24578, XP002101936.

Other Reference Publication - OREF (6):
Leung D.W. et al.: "Molecular cloning of two alternatively spliced forms of human phosphatidic acid phosphatase cDNA that are differently expressed in normal tumor cells" DNA Cell Biology, vol. 17, No. 4, Apr. 1998 (Apr. 1998), pp. 377-385, XP002101937.

US-PAT-NO: 6133274

DOCUMENT-IDENTIFIER: US 6133274 A

TITLE: Hydroxyl-containing bicyclic compounds

DATE-ISSUED: October 17, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Underiner; Gail E.	Brier	WA	N/A	N/A
Porubek; David	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Woodson; Paul	Edmonds	WA	N/A	N/A

APPL-NO: 08/ 756703

DATE FILED: November 26, 1996

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a continuation application of Ser. No. 08/153,256 filed Nov. 16, 1993 which is abandoned, which in turn is a continuation-in-part application of Ser. No. 07/976,353 filed Nov. 16, 1992, now U.S. Pat. No. 5,473,070.

US-CL-CURRENT: 514/263.36, 544/267

ABSTRACT:

Disclosed are therapeutic compounds having the formula:

(R)j-(core moiety),

including resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is either non-cyclic or comprises at least one five- to seven-membered ring structure, R may be selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, C.sub.1-6 alkyl or C.sub.1-6 alkenyl, and at least one R has the formula I: ##STR1## n is an integer from seven to twenty and at least one of X or Y is --OH. The other of X or Y, which is not --OH, is hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --, and each W.sub.1, W.sub.2, and W.sub.3 is independently hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --. The X, Y, W.sub.1, W.sub.2, or W.sub.3 alkyl groups may be unsubstituted or substituted by an hydroxyl, halo or dimethylamino group. The disclosed compounds and therapeutic compositions thereof are useful in treating individuals having a disease or treatment-induced toxicity, mediated by second messenger activity.

13 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

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Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 6103730

DOCUMENT-IDENTIFIER: US 6103730 A

TITLE: Amine substituted compounds

DATE-ISSUED: August 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A
Ridgers; Lance H.	Bothell	WA	N/A	N/A

APPL-NO: 08/ 486264

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

This is a Continuation in Part of U.S. application Ser. No. 08/217,051, filed Mar. 24, 1994 ABN.

US-CL-CURRENT: 514/263.2, 514/151 , 514/210.21 , 514/263.21 , 514/263.22 , 514/263.23 , 514/263.24 , 514/263.35 , 544/268 , 544/269 , 544/270 , 544/271 , 544/272

ABSTRACT:

Compounds and pharmaceutical compositions, including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof, have the formula:

CORE MOIETY--(R).sub.j

In these compounds, j is an integer from one to three; the core moiety is a cyclic core, the cyclic core being non-cyclic or at least one five- to seven-member non-heterocyclic ring or heterocycle; and R is selected from the group consisting of amine, hydrogen, halogen, hydroxyl, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic group or formula I. At least one R having formula I: ##STR1## In formula I, n is an integer from four to twenty; and each R.sub.1 or R.sub.2 is independently hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or cyclic or heterocyclic group. The compounds are useful in treating or preventing, for example, sepsis syndrome, hematopoietic or organ toxicity, cancer, viral activity, AIDS and AIDS-related indications, allopecia caused by cytotoxic therapies, and progression of an inflammatory or autoimmune disease.

7 Claims, 23 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 23

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Detailed Description Text - DETX (2):
The inventive compounds may control cell behavior by a particular phase of a second messenger pathway system (Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem. Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and proteins and use the following abbreviations:

Detailed Description Text - DETX (21):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase (PAPH) within 5 seconds of cell (for example, human mesangial cells, HMC) exposure. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT (1,2-sn-dilinoleoyl PA) activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol and 1-o-alkyl, or 1-o-alkenyl, acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

Other Reference Publication - OREF (5):
Bursten et al., The Journal of Biological Chemistry, vol. 266, No. 31, pp. 20732-20743, "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase activities in Human Mesangial Cells", Nov. 1991.

US-PAT-NO: 6100271

DOCUMENT-IDENTIFIER: US 6100271 A

TITLE: Therapeutic compounds containing xanthinyl

DATE-ISSUED: August 8, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Leigh; Alistair J.	Brier	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 483871

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a Continuation-in-Part patent application of U.S. patent application Ser. No. 08/199,368, which was filed on Feb. 18, 1994 and which is now abandoned.

US-CL-CURRENT: 514/263.2, 514/210.21 , 514/234.2 , 514/263.22 , 514/263.23 , 514/263.24 , 514/263.35 , 544/268 , 544/269 , 544/271

ABSTRACT:

Therapeutic compounds with at least one carboxylic acid, ester or amide-substituted side chain have the formula:

CORE MOIETY --(R).sub.j

wherein j is an integer from one to three. The core moiety is non-cyclic or cyclic (carbocyclic or heterocyclic). R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, carbocyclic or heterocyclic groups and at least one R has the formula I: ##STR1## wherein: one or two p are the integer one, otherwise p is two; and n is an integer from three to twenty; R.sub.1 is selected from the group consisting of substituted and unsubstituted CH.sub.2 ; NR.sub.3, R.sub.3 being hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or C.sub.(1-20) hydroxyalkyl, or carbocyclic or heterocyclic group; O; --CHR.sub.4 O--, R.sub.4 being substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl, C.sub.(1-20) hydroxyalkyl, or R.sub.2 and R.sub.4 join to form a substituted or unsubstituted heterocycle having four to seven ring atoms, the ether group --O-- of --CHR.sub.4 O-- being a member of the heterocycle. R.sub.2 is selected from the group consisting of hydrogen; halogen; substituted or unsubstituted C.sub.(1-10) alkyl; C.sub.(1-10) alkoxyl; C.sub.(2-10) alkenyl; C.sub.(1-10) hydroxyallyl; --A(R.sub.5).sub.m, A being N or O, m being one or two and R.sub.5 being hydrogen, a substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxyl, C.sub.(2-10) alkenyl or C.sub.(1-10) hydroxyalkyl), or carbocyclic or heterocyclic group. At least one of R.sub.1

is NR.sub.3, O or --CHR.sub.4 O--, or R.sub.2 is --A(R.sub.5).sub.m. The compounds and pharmaceutical compositions thereof are useful as therapies for diseases advanced via intracellular signaling through specific intracellular signaling pathways by mediating a signaling response to an external stimuli.

14 Claims, 5 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

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Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. As discussed in detail above, activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl, or 1-o-alkenyl,acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 6043250

DOCUMENT-IDENTIFIER: US 6043250 A

TITLE: Methods for using therapeutic compounds containing xanthinyl

DATE-ISSUED: March 28, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Leigh; Alistair J.	Brier	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A
Rice; Glenn C.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 472296

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a Continuation-in-Part patent application of U.S. patent application Ser. No. 08/199,368, which was filed on Feb. 18, 1994, now abandoned.

US-CL-CURRENT: 514/234.2, 514/210.21 , 514/263.2 , 514/263.22 , 514/263.23 , 514/263.35

ABSTRACT:

Therapeutic compounds with at least one carboxylic acid, ester or amide-substituted side chain have the formula:

CORE MOIETY --(R).sub.j

wherein j is an integer from one to three. The core moiety is non-cyclic or cyclic (carbocyclic or heterocyclic). R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C(.sub.1-10) alkyl, C(.sub.2-10) alkenyl, carbocyclic or heterocyclic groups and at least one R has the formula I: ##STR1## wherein: one or two p are the integer one, otherwise p is two; and n is an integer from three to twenty; R.sub.1 is selected from the group consisting of substituted and unsubstituted CH.sub.2 ; NR.sub.3, R.sub.3 being hydrogen, substituted or unsubstituted C(.sub.1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or C.sub.(1-20) hydroxyalkyl, or carbocyclic or heterocyclic group; O; --CHR.sub.4 O--, R.sub.4 being substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl, C.sub.(1-20) hydroxyalkyl, or R.sub.2 and R.sub.4 join to form a substituted or unsubstituted heterocycle having four to seven ring atoms, the ether group --O-- of --CHR.sub.4 O-- being a member of the heterocycle. R.sub.2 is selected from the group consisting of hydrogen; halogen; substituted or unsubstituted C.sub.(1-10) alkyl; C.sub.(1-10) alkoxyl; C.sub.(2-10) alkenyl; C.sub.(1-10) hydroxyalkyl; --A(R.sub.5).sub.m, A being N or 0, m being one or two and R.sub.5 being hydrogen, a substituted or unsubstituted C.sub.(1-10)

alkyl, C.sub.(1-10) alkoxyl, C.sub.(2-10) alkenyl or C.sub.(1-10) hydroxyalkyl), or carbocyclic or heterocyclic group. At least one of R.sub.1 is NR.sub.3, O or --CHR.sub.4 O--, or R.sub.2 is --A(R.sub.5).sub.m. The compounds and pharmaceutical compositions thereof are useful as therapies for diseases advanced via intracellular signaling through specific intracellular signaling pathways by mediating a signaling response to an external stimuli.

6 Claims, 0 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

---------- KWIC ---------

Detailed Description Text - DETX (38):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure to this cytokine. As discussed in detail above, activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl, or 1-o-alkenyl,acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 6020337

DOCUMENT-IDENTIFIER: US 6020337 A

TITLE: Electronegative-substituted long chain xanthine compounds

DATE-ISSUED: February 1, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Leigh; Alistair J.	Brier	WA	N/A	N/A
Michnick; John	Seattle	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail	Malvern	PA	N/A	N/A

APPL-NO: 08/ 950810

DATE FILED: September 16, 1997

PARENT-CASE:

This is a Continuation-in-Part Application of U.S. applications Ser. No. 08/042,946, now U.S. Pat. No. 5,670,506, and Ser. No. 08/910,579, filed Apr. 5, 1993 and Jul. 26, 1997, respectively.

US-CL-CURRENT: 514/263.34, 514/210.21 , 514/263.36 , 544/267 , 544/272 , 544/277

ABSTRACT:

Therapeutic compounds, including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof, having a formula: ##STR1## wherein R.sub.0 is selected from the group consisting of hydrogen, halo, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic groups, wherein the substituents of substituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl are other than halo; n is an integer from one to sixteen; R.sub.1, R.sub.2, and R.sub.3 are independently selected from the group consisting of a halo; haloacetoxy; hydrogen; hydroxy; oxo; --N.dbd.C.dbd.S; --N.dbd.C.dbd.O; --0--C.tbd.N; --C.tbd.N; --N.dbd.N.dbd.N; and --C--(R.sub.5).sub.3, R.sub.5 being independently a halo or hydrogen, at least one R.sub.5 being halo, at least one of R.sub.1, R.sub.2, and R.sub.3 being halo, cyano, isocyano, isothiocyano, azide or haloacetoxy group; R.sub.4 is hydrogen, C.sub.(1-6) alkyl, C.sub.(1-6) alkenyl, cyclo C.sub.(4-6) alkyl, or phenyl; one or more hydrogen atoms of (CH.sub.2).sub.n --CH.sub.a --CH.sub.b --CH.sub.c may be replaced with: i) at least one of halogen atom, hydroxyl, oxo, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxyalkyl, or C.sub.(2-10) alkenyl; or ii) one or more unsaturated bonds; and any two adjacent carbon atoms of (CH.sub.2).sub.n --CH.sub.a --CH.sub.b --CH.sub.c may be instead separated by at least one oxygen atom. These compounds are useful in treating or preventing diseases by inhibiting selective second messenger pathways.

17 Claims, 16 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 16

---------- KWIC --------

Detailed Description Text - DETX (2):
The inventive compounds may control cell behavior by a particular phase of a second messenger pathway system (Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

Detailed Description Text - DETX (21):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase (PAPH) within 5 seconds of cell (for example, human mesangial cells, HMC) exposure. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT (1,2-sn-dilinoleoyl PA) activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol and 1-o-alkyl, or 1-o-alkenyl, acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5889011

DOCUMENT-IDENTIFIER: US 5889011 A
See image for Certificate of Correction

TITLE: Substituted amino alkyl compounds

DATE-ISSUED: March 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Leigh; Alistair J.	Brier	WA	N/A	N/A

APPL-NO: 08/ 884037

DATE FILED: June 27, 1997

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation application of Ser. No. 08/149,681 filed Nov. 9, 1993, now abandoned which in turn is a continuation-in-part of application Ser. No. 07/973,804 filed Nov. 9, 1992 now U.S. Pat. No. 5,340,813.

US-CL-CURRENT: 514/263.35, 544/264 , 544/265 , 544/267

ABSTRACT:

Compounds and pharmaceutical compositions thereof comprise the formula:

(R)j- (core moiety),

including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof, wherein J is an integer from one to three, the core moiety is non-cyclic or comprises at least one, five- to seven-membered ring structure, R may be selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, alkyl (C.sub.1-6) or alkenyl (C.sub.1-6), and at least one R has the formula I: ##STR1## wherein n is an integer from four to eighteen; each R'.sub.1 and R'.sub.2 is independently hydrogen, alkyl (C.sub.1-4) or alkenyl (C.sub.1-4), the alkyl or alkenyl groups being preferably substituted by a halogen, hydroxyl, ketone or dimethylamino group and/or may be interrupted by an oxygen or hydrogen atom or an alkyl (C.sub.1-4) group; and each R'.sub.3 and R'.sub.4 is independently hydrogen or methyl. Preferably, n is an integer from six to ten, R'.sub.1 and R'.sub.2 are independently hydrogen or methyl and R'.sub.3 and R'.sub.4 are hydrogen. The compounds are useful in treating or preventing, for example, sepsis syndrome, hematopoietic or organ toxicity, baldness, hair loss or allopecia caused by cytotoxic therapies, and progression of an inflammatory or autoimmune disease.

9 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC --------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

Other Reference Publication - OREF (3):

Bursten et al., The Journal of Biological Chemistry, vol. 266, No. 31, pp. 20732-20743, "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase activities in Human Mesangial Cells", Nov. 1991.

US-PAT-NO: 5888793

DOCUMENT-IDENTIFIER: US 5888793 A

TITLE: Human lysophosphatidic acid acyltransferase

DATE-ISSUED: March 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hillman; Jennifer L.	Mountain View	CA	N/A	N/A
Yue; Henry	Sunnyvale	CA	N/A	N/A
Guegler; Karl J.	Menlo Park	CA	N/A	N/A
Corley; Neil C.	Mountain View	CA	N/A	N/A

APPL-NO: / 030652

DATE FILED: February 25, 1998

US-CL-CURRENT: 435/193, 435/252.3 , 435/252.33 , 435/254.11 , 435/254.3 , 435/320.1 , 435/325 , 435/419 , 435/6 , 536/23.2

ABSTRACT:

The invention provides a human lysophosphatidic acid acyltranferase (HLPAAT) and polynucleotides which identify and encode HLPAAT. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for treating or preventing disorders associated with expression of HLPAAT.

9 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

---------- KWIC ---------

Other Reference Publication - OREF (6):
Bursten SL, et al. Interleukin-1 rapidly stimulates lysophosphatidate acyltransferase and phosphatidate phosphohydrolase activities in human mesangial cells. J Biol Chem. 1991 Nov. 5; 266(31): 20732-20743.

US-PAT-NO: 5856115

DOCUMENT-IDENTIFIER: US 5856115 A

TITLE: Assay for identification therapeutic agents

DATE-ISSUED: January 5, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bianco; James A.	Seattle	WA	N/A	N/A
Bursten; Stuart L.	Snoqualmie	WA	N/A	N/A
Singer; Jack W.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 196878

DATE FILED: February 14, 1994

PARENT-CASE:

This is a Continuation of application No. Ser. 07/888,722, filed May 26, 1992, now abandoned which in turn is a continuation-in-part of application No. Ser. 07/732,227, filed Jul. 16, 1991, now abandoned which is a continuation-in-part of application No. Ser. 07/704,992, filed on May 24, 1991 now abandoned.

US-CL-CURRENT: 435/15, 424/85.1 , 514/263.36

ABSTRACT:

There is disclosed a method for screening for inhibitors of cellular second messenger signaling regulated by lysophosphatidic acid acyl transferase (LPAAT) and phosphatidic acid phosphohydrolase (PAPH), which method comprises contacting target cells or appropriate subcullular elements under appropriate conditions of stimulation with a candidate drug and assessing the levels of the relevant subsets of phosphatidic acid (PA) and diacylglycerol (DAG) in the presence and absence of the candidate drug.

4 Claims, 27 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 22

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Detailed Description Text - DETX (123):
We are claiming that renal side effects (hyperkalemia, localized renal hypertension) and diffuse systemic effects possibly growing out of this renal effect (e.g., hypertension) are derived from stimulation of our pathway in renal mesangial cells and diffusely in endothelial cells; that is to say, a side effect of cyclosporine, due to its membrane active/lipid soluble attributes, is stimulation of lyso-PA acyl transferase and **phosphatidate phosphohydrolase (there is direct data available on this from human** mesangial cells, endothelial cells, and 3T3 fibroblasts).

US-PAT-NO: 5837703

DOCUMENT-IDENTIFIER: US 5837703 A

TITLE: Amino-alcohol substituted cyclic compounds

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kumar; Anil M.	Seattle	WA	N/A	N/A
Michnick; John	Seattle	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Rice; Glenn C.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 152650

DATE FILED: November 12, 1993

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION

This application is a Continuation-in-Part Application of U.S. application Ser. No. 08/040,820 filed Mar. 31, 1993, now abandoned.

US-CL-CURRENT: 514/183, 514/211.15 , 514/228.8 , 514/241 , 514/242 , 514/249 , 514/256 , 514/266.2 , 514/266.3 , 514/270 , 514/274 , 514/309 , 514/312 , 514/315 , 514/348 , 514/357 , 514/374 , 514/400 , 514/425 , 514/427 , 540/467 , 540/544 , 544/216 , 544/257 , 544/272 , 544/286 , 544/301 , 544/311 , 544/335 , 546/141 , 546/142 , 546/157 , 546/246 , 546/296 , 546/334 , 546/96 , 548/215 , 548/340.1 , 548/485 , 548/546 , 548/561

ABSTRACT:

Therapeutic compounds have the formula:

(X)j-(core moiety),

j being an integer from one to three, the core moiety comprising a core moiety, the core moiety being a heterocycle having one ring or two-fused rings, each ring having five or six ring atoms, A being a carbon atom of the core moiety and attached to a terminal carbon atom of (CH.sub.2).sub.m, and X has a structure and X being a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of: ##STR1## *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkyl or alkenyl of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxyl. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3.

Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a straight or branched chain alkyl or alkenyl of up to eight carbon atoms in length, –(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxyl, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxyl group.

9 Claims, 39 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 38

---------- KWIC ---------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5824677

DOCUMENT-IDENTIFIER: US 5824677 A

TITLE: Substituted amino alcohol compounds

DATE-ISSUED: October 20, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 474816

DATE FILED: June 7, 1995

PARENT-CASE:

This is a Division of U.S. application Ser. No. 08/303,842, filed Sep. 8, 1994, now U.S. Pat. No. 5,641,783, which is a Continuation-in-Part of application Nos. 08/152,650, filed Nov. 12, 1993, now U.S. Pat. No. 5,801,181, and 08/164,081, filed Dec. 8, 1993, now U.S. Pat. No. 5,470,878, which are Continuation-in-Part Applications of application No. 08/040,820, filed Mar. 31, 1993 now abandoned.

US-CL-CURRENT: 514/222.5, 514/223.5 , 514/224.5 , 514/226.8 , 514/227.5 , 514/228.8 , 514/229.2 , 514/230.5 , 514/230.8 , 514/237.8 , 514/248 , 514/249 , 514/255.02 , 514/260.1 , 514/274 , 514/301 , 514/303 , 514/311 , 514/351 , 514/360 , 514/361 , 514/362 , 514/363 , 514/364 , 514/365 , 514/367 , 514/372 , 514/373 , 514/374 , 514/375 , 514/376 , 514/378 , 514/379 , 514/380 , 514/387 , 514/395 , 514/415 , 514/418 , 514/424 , 514/425 , 514/432 , 514/433 , 514/438 , 514/452 , 544/127 , 544/128 , 544/162 , 544/2 , 544/215 , 544/219 , 544/229 , 544/235 , 544/237 , 544/255 , 544/278 , 544/3 , 544/311 , 544/353 , 544/385 , 544/5 , 544/53 , 544/63 , 544/65 , 544/66 , 544/67 , 544/8 , 544/90 , 544/91 , 546/113 , 546/114 , 546/164 , 546/300 , 548/123 , 548/125 , 548/131 , 548/134 , 548/143 , 548/146 , 548/153 , 548/174 , 548/207 , 548/214 , 548/215 , 548/217 , 548/221 , 548/228 , 548/229 , 548/237 , 548/240 , 548/241 , 548/243 , 548/247 , 548/267.2 , 548/303.7 , 548/307.1 , 548/453 , 548/486 , 548/543 , 548/546 , 549/14 , 549/367 , 549/368 , 549/50 , 549/75

ABSTRACT:

Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated

heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocyle. R.sub.3 may be either hydrogen or C.sub.13. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a hetorocycle comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

18 Claims, 120 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 89

---------- KWIC ---------

Detailed Description Text - DETX (2):

The invention provides a genus of compounds which can control cellular behavior by a particular phase of a secondary messenger pathway system (Bursten et al, "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

US-PAT-NO: 5817662

DOCUMENT-IDENTIFIER: US 5817662 A

TITLE: Substituted amino alkyl compounds

DATE-ISSUED: October 6, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Leigh; Alistair J.	Brier	WA	N/A	N/A

APPL-NO: 08/ 468656

DATE FILED: June 6, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

This is a Divisional of U.S. patent application Ser. No. 08/149,681, filed Nov. 9, 1993, on which in turn is a Continuation-in-Part Application of U.S. patent application Ser. No. 07/973.804, filed Nov. 9, 1992, now U.S. Pat. No. 5,340,813.

US-CL-CURRENT: 514/263.35, 424/824 , 424/825

ABSTRACT:

Compounds and pharmaceutical compositions thereof comprise the formula:

(R)j-(core moiety),

including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof, wherein J is an integer from one to three, the core moiety is non-cyclic or comprises at least one, five- to seven-membered ring structure, R may be selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, alkyl (C.sub.1-6) or alkenyl (C.sub.1-6), and at least one R has the formula I: ##STR1## wherein n is an integer from four to eighteen; each R'.sub.1 and R'.sub.2 is independently hydrogen, alkyl (C.sub.1-4) or alkenyl (C.sub.1-4), the alkyl or alkenyl groups being preferably substituted by a halogen, hydroxyl, ketone or dimethylamino group and/or may be interrupted by an oxygen or hydrogen atom or an alkyl (C.sub.1-4) group; and each R'.sub.3 and R'.sub.4 is independently hydrogen or methyl. Preferably, n is an integer from six to ten, R'.sub.1 and R'.sub.2 are independently hydrogen or methyl and R'.sub.3 and R'.sub.4 are hydrogen. The compounds are useful in treating or preventing, for example, sepsis syndrome, hematopoietic or organ toxicity, baldness, hair loss or allopecia caused by cytotoxic therapies, and progression of an inflammatory or autoimmune disease.

7 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

Other Reference Publication - OREF (3):

Bursten et al., The Journal of Biological Chemistry, vol. 266, No. 31, pp. 20732-20743, "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase activities in Human Mesangial Cells", Nov., 1991.

US-PAT-NO: 5807862

DOCUMENT-IDENTIFIER: US 5807862 A
See image for Certificate of Correction

TITLE: Therapeutic compounds containing pyrimidinyl moieties

DATE-ISSUED: September 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Leigh; Alistair J.	Brier	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 478112

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION

This is a Continuation-in-Part patent application of U.S. patent application Ser. No. 08/199,368, which was filed on Feb. 18, 1994 abandoned.

US-CL-CURRENT: 514/269, 544/309 , 544/310 , 544/311 , 544/312

ABSTRACT:

Therapeutic compounds with at least one carboxylic acid, ester or amide-substituted side chain have the formula:

CORE MOIETY--(R).sub.j

wherein j is an integer from one to three. The core moiety is non-cyclic or cyclic (carbocyclic or heterocyclic). R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, carbocyclic or heterocyclic groups and at least one R has the formula I: ##STR1## wherein: one or two p are the integer one, otherwise p is two; and n is an integer from three to twenty; R.sub.1 is selected from the group consisting of substituted and unsubstituted CH.sub.2 ; NR.sub.3, R.sub.3 being hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or C.sub.(1-20) hydroxyalkyl, or carbocyclic or heterocyclic group; O; --CHR.sub.4 O--, R.sub.4 being substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl, C.sub.(1-20) hydroxyalkyl, or R.sub.2 and R.sub.4 join to form a substituted or unsubstituted heterocycle having four to seven ring atoms, the ether group --O-- of --CHR.sub.4 O-- being a member of the heterocycle. R.sub.2 is selected from the group consisting of hydrogen; halogen; substituted or unsubstituted C.sub.(1-10) alkyl; C.sub.(1-10) alkoxyl; C.sub.(2-10) alkenyl; C.sub.(1-10) hydroxyalkyl; --A(R.sub.5).sub.m, A being N or O, m being one or two and R.sub.5 being hydrogen, a substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxyl, C.sub.(2-10) alkenyl or C.sub.(1-10) hydroxyalkyl), or carbocyclic or heterocyclic group. At least one of R.sub.1 is NR.sub.3, O or --CHR.sub.4 O--, or R.sub.2 is --A(R.sub.5).sub.m. The

compounds and pharmaceutical compositions thereof are useful as therapies for diseases advanced via intracellular signaling through specific intracellular signaling pathways by mediating a signaling response to an external stimuli.

6 Claims, 5 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

---------- KWIC ---------

Detailed Description Text - DETX (39):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure to this cytokine. As discussed in detail above, activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl, or 1-o-alkenyl,acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflainmatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5807861

DOCUMENT-IDENTIFIER: US 5807861 A
See image for Certificate of Correction

TITLE: Amine substituted xanthinyl compounds

DATE-ISSUED: September 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A
Ridgers; Lance H.	Bothell	WA	N/A	N/A
Rice; Glenn C.	Seattle	WA	N/A	N/A
Leung; David W.	Mercer Island	WA	N/A	N/A

APPL-NO: 08/ 476911

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

This is a Continuation in Part of U.S. application Ser. No. 08/217,051, filed Mar. 24, 1994, abandoned.

US-CL-CURRENT: 514/263.35, 514/151 , 514/210.21 , 514/263.2 , 514/263.22 , 514/263.23 , 514/81

ABSTRACT:

A method for treating a disease caused by an undesirable cell response mediated by a proliferative intracellular signaling pathway is provided wherein an effective amount of a compound is administered. The compound, resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof, has the formula

CORE MOIETY--(R).sub.j

wherein j is an integer from one to three; the core moiety is xanthinyl; and R is independently selected from the group consisting of amine, hydrogen, halogen, hydroxyl, C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, 2-bromopropyl, 4-chloropentyl, cyclohexyl, cyclopentyl, 3-dimethylaminobutyl, 2-hydroxyethyl, 5-hydroxyhexyl, 3-hydroxy-n-butyl, 3-hydroxypropyl, 2-methoxyethyl, 4-methoxy-n-butyl, phenyl, and formula I, at least one R comprising formula I ##STR1## wherein (CH.sub.2).sub.n is optionally substituted; n is an integer from five to twenty; each R.sub.1 or R.sub.2 is independently hydrogen or an optionally substituted group that is herein defined; and

wherein, when the (CH.sub.2).sub.n, R.sub.1 or R.sub.2 is substituted, a substituent is selected from the group consisting of carbamoyl, primary, secondary and tertiary amino, C.sub.(2-8) alkenyl, C.sub.(1-8) alkyl, C.sub.(1-8) alkoxyl, C.sub.(1-8) hydroxyalkyl, azido, carbonato, carbonyl, carboxyl, cyano, C.sub.(1-8) haloalkyl, isocyano, isomercaptocyano, phospho,

phosphonato, sulfonato, alkylsulfonyl, alkylsulfoxidyl, mercaptocarbonyl, mercaptocarbonato, thioureido and ureido.

21 Claims, 23 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 23

---------- KWIC ---------

Detailed Description Text - DETX (2):
The inventive compounds may control cell behavior by a particular phase of a second messenger pathway system (Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and **Phosphatidate Phosphohydrolase Activities in Human** Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

Detailed Description Text - DETX (21):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase (PAPH) within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure. Activation of both enzymes results in production of PA species with sn-i and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT (1,2-sn-dilinoleoyl PA) activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol and 1-o-alkyl, or 1-o-alkenyl, acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5804584

DOCUMENT-IDENTIFIER: US 5804584 A
See image for Certificate of Correction

TITLE: Therapeutic compounds containing a monocyclic five- to six- membered ring structure having one to two nitrogen atoms

DATE-ISSUED: September 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Underiner; Gail E.	Brier	WA	N/A	N/A
Porubek; David	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Woodson; Paul	Edmonds	WA	N/A	N/A

APPL-NO: 08/ 468659

DATE FILED: June 6, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a Divisional of U.S. patent application Ser. No. 07/153,256, filed Nov. 16, 1993 now abandoned, which in turn is a Continuation-In-Part of U.S. patent application Ser. No. 07/976,353, filed Nov. 16, 1992 now patented U.S. Pat. No. 5,473,070.

US-CL-CURRENT: 514/269, 514/256 , 544/242 , 544/298 , 544/301 , 544/302

ABSTRACT:

Disclosed are therapeutic compounds having the formula:

(R)j-(core moiety),

including resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is either non-cyclic or comprises at least one five- to seven-membered ring structure, R may be selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, C.sub.1-6 alkyl or C.sub.1-6 alkenyl, and at least one R has the formula I: ##STR1## n is an integer from seven to twenty and at least one of X or Y is --OH. The other of X or Y, which is not --OH, is hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --, and each W.sub.1, W.sub.2, and W.sub.3 is independently hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --. The X, Y, W.sub.1, W.sub.2, or W.sub.3 alkyl groups may be unsubstituted or substituted by an hydroxyl, halo or dimethylamino group. The disclosed compounds and therapeutic compositions thereof are useful in treating individuals having a disease or treatment-induced toxicity, mediated by second messenger activity.

9 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

---------- KWIC ---------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and i-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5801182

DOCUMENT-IDENTIFIER: US 5801182 A

TITLE: Amine substituted compounds

DATE-ISSUED: September 1, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A
Ridgers; Lance H.	Bothell	WA	N/A	N/A

APPL-NO: 08/ 485777

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

This is a Continuation in Part of U.S. application Ser. No. 08/217,051, filed Mar. 24, 1994 now abandoned.

US-CL-CURRENT: 514/269, 514/274 , 544/310 , 544/311 , 544/312

ABSTRACT:

Compounds and pharmaceutical compositions, including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof, have the formula:

CORE MOIETY --(R).sub.j

In these compounds, j is an integer from one to three; the core moiety is a cyclic core, the cyclic core being non-cyclic or at least one five- to seven-member non-heterocyclic ring or heterocycle; and R is selected from the group consisting of amine, hydrogen, halogen, hydroxyl, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic group or formula I. At least one R having formula I: ##STR1## In formula I, n is an integer from four to twenty; and each R.sub.1 or R.sub.2 is independently hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or cyclic or heterocyclic group. The compounds are useful in treating or preventing, for example, sepsis syndrome, hematopoietic or organ toxicity, cancer, viral activity, AIDS and AIDS-related indications, allopecia caused by cytotoxic therapies, and progression of an inflammatory or autoimmune disease.

16 Claims, 23 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 23

---------- KWIC --------

Detailed Description Text - DETX (2):

The inventive compounds may control cell behavior by a particular phase of a second messenger pathway system (Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and proteins use the following abbreviations:

Detailed Description Text - DETX (21):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase (PAPH) within 5 seconds of cell (for example, human mesangial cells, HMC) exposure. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT (1,2-sn-dilinoleoyl PA) activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol and 1-o-alkyl, or 1-o-alkenyl, acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5801181

DOCUMENT-IDENTIFIER: US 5801181 A

TITLE: Amino alcohol substituted cyclic compounds

DATE-ISSUED: September 1, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Michnick; John	Seattle	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Rice; Glenn C.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 474820

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a Division of U.S. application Ser. No. 08/152,650, filed Nov. 12, 1993 now abandoned which is a Continuation-in-Part Application of U.S. application Ser. No. 08/040,820 filed Mar. 31, 1993.

US-CL-CURRENT: 514/263.35, 514/183 , 514/249 , 514/266.3 , 514/274 , 514/309 , 514/315 , 514/418 , 514/425 , 514/617 , 514/619 , 514/626 , 514/668 , 514/669

ABSTRACT:

Therapeutic compounds have the formula:

(X)j--(core moiety),

J being an integer from one to three, the core moiety having at least one, five- to seven-membered ring and X being a racemic mixture, R or S enantiomer, slovate, hydrate, or salt of: ##STR1## *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3. Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon

atoms, N being a hetero atom. r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxy group.

45 Claims, 41 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 38

---------- KWIC ---------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5780476

DOCUMENT-IDENTIFIER: US 5780476 A

TITLE: Hydroxyl-containing xanthine compounds

DATE-ISSUED: July 14, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Underiner; Gail E.	Brier	WA	N/A	N/A
Porubek; David	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Woodson; Paul	Edmonds	WA	N/A	N/A

APPL-NO: 08/ 468660

DATE FILED: June 6, 1995

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION

This is a Divisional of U.S. patent application Ser. No. 07/153,256, filed Nov. 16, 1993 now abandoned, which in turn is a Continuation-In-Part of U.S. patent application Ser. No. 07/976,353, filed Nov. 16, 1992 now U.S. Pat. No. 5,473,070.

US-CL-CURRENT: 514/263.36

ABSTRACT:

Disclosed are therapeutic compounds having the formula:

(R)j - (core moiety),

including resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is either non-cyclic or comprises at least one five- to seven-membered ring structure, R may be selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, C.sub.1-6 alkyl or C.sub.1-6 alkenyl, and at least one R has the formula I: ##STR1## n is an integer from seven to twenty and at least one of X or Y is --OH. The other of X or Y, which is not --OH, is hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --, and each W.sub.1, W.sub.2, and W.sub.3 is independently hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --. The X, Y, W.sub.1, W.sub.2, or W.sub.3 alkyl groups may be unsubstituted or substituted by an hydroxyl, halo or dimethylamino group. The disclosed compounds and therapeutic compositions thereof are useful in treating individuals having a disease or treatment-induced toxicity, mediated by second messenger activity.

11 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

---------- KWIC ---------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5777117

DOCUMENT-IDENTIFIER: US 5777117 A

TITLE: Method for preparing substituted amino alcohol compounds

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 472569

DATE FILED: June 7, 1995

PARENT-CASE:

This is a Division of U.S. application Ser. No. 08/303,842, filed Sep. 8, 1994, which is a Continuation-in-Part of application Ser. Nos. 08/152,650, filed Nov. 12, 1993 and 08/164,081, filed Dec. 8, 1993, which are Continuation-in-Part Applications of application Ser. No. 08/040,820, filed Mar. 31, 1993, now abandoned.

US-CL-CURRENT: 544/267, 544/257 , 544/285 , 544/286 , 544/287 , 544/311 , 546/141 , 546/243 , 546/246 , 548/477 , 548/546

ABSTRACT:

Disclosed is a process for preparing compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocyle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a terminal moiety comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

22 Claims, 118 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 92

---------- KWIC --------

Detailed Description Text - DETX (2):

The invention provides a genus of compounds which can control cellular behavior by a particular phase of a secondary messenger pathway system (Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

US-PAT-NO: 5777115

DOCUMENT-IDENTIFIER: US 5777115 A

TITLE: Acetal-and ketal-substituted pyrimidine compounds

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Leigh; Alistair	Brier	WA	N/A	N/A
Underiner; Gail	Brier	WA	N/A	N/A

APPL-NO: 08/ 193331

DATE FILED: February 7, 1994

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a continuation-in-part application of U.S. application Ser. No. 08/004,353, filed Jan. 14, 1993 now abandoned.

US-CL-CURRENT: 544/242, 544/267

ABSTRACT:

Acetal-and ketal-substituted compounds and pharmaceutical compositions thereof have the following formula:

CORE MOIETY--(R).sub.j,

including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is non-cyclic or cyclic a monocyclic moiety having at least one nitrogen atom within the ring and R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted alkyl C.sub.(1-6), alkenyl C.sub.(2-6), cyclic or heterocyclic groups, and groups having a structure prescribed by formula I. At least one R has the formula I:

--(CH.sub.2).sub.n --C--(R.sub.1).sub.3 I

wherein n is an integer from three to twenty; R.sub.1 is selected from among hydrogen; halogen; hydroxide; substituted or unsubstituted C.sub.(1-6) alkyl, C.sub.(1-6) alkoxy, C.sub.2-6) alkenyl, cyclic or heterocyclic group; --OR.sub.2, R.sub.2 being hydrogen or a substituted or unsubstituted C.sub.(1-6) alkyl, C.sub.(2-6) alkenyl, cyclic or heterocyclic group; --(CH.sub.2).sub.p --C(R.sub.3).sub.3 (wherein p is zero or an integer from one to ten, R.sub.3 is hydrogen, halogen, hydroxide, substituted or unsubstituted C.sub.(1-6) alkyl, C.sub.(1-6) alkoxy, C.sub.(2-6) alkenyl, cyclic or heterocyclic group, or --OR.sub.2, R.sub.2 being defined above). The inventive compounds are useful in a large variety of therapeutic indications for treating or preventing disease mediated by intracellular signaling through specific intracellular signaling pathways.

13 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

---------- KWIC --------

Detailed Description Text - DETX (39):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure to this cytokine. As discussed in detail above, activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl, or 1-o-alkenyl,acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5770595

DOCUMENT-IDENTIFIER: US 5770595 A

TITLE: Oxime substituted therapeutic compounds

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Leigh; Alistair	Brier	WA	N/A	N/A

APPL-NO: 08/ 193344

DATE FILED: February 7, 1994

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This is a Continuation-in-Part Application of U.S. application Ser. No. 08/006,083, filed Jan. 19, 1993.

US-CL-CURRENT: 514/263.35, 514/151 , 544/271 , 544/273

ABSTRACT:

Oxime-substituted compounds are preferably cyclic or heterocyclic compounds. The oxime-substituted compounds and pharmaceutical compositions thereof have the formula:

CORE MOIETY--(R).sub.j

including resolved enantiomers (both syn and anti forms) and/or diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is non-cyclic or cyclic and R may be selected from among: hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10), alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic groups, and formula I. At least one R has the formula I:

--(CH.sub.2).sub.n --C--(R.sub.1).sub.p, I

wherein n is an integer from three to twenty; p is two or three; R.sub.1 is selected from among hydrogen; halogen; hydroxide; substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxy, C.sub.(2-10) alkenyl, cyclic or heterocyclic group; =N--OR.sub.2, R.sub.2 being hydrogen or a substitute or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic group; and --(CH.sub.2).sub.s --C(R.sub.3).sub.t (wherein s is zero or an integer from one to ten, t is two or three, R.sub.3 is hydrogen, halogen, hydroxide, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxy, C(.sub.2-10) alkenyl, cyclic or heterocyclic group, or .dbd.N--OR.sub.2, R.sub.2 being defined above). At least one R.sub.1 or one R.sub.3 is .dbd.N--OR.sub.2, p or t corresponding to the at least one R.sub.1 or one R.sub.3 is two, and a second R.sub.1 or second R.sub.3, bonded to the same --C as the at least one R.sub.1 or one R.sub.3, is other than .dbd.N--OR.sub.2. These disclosed compounds are useful in a large variety of

therapeutic indications for treating or preventing disease mediated by intracellular signaling through specific intracellular signaling pathways.

22 Claims, 19 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 19

---------- KWIC --------

Detailed Description Text - DETX (39):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. As discussed in detail above, activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl, or 1-o-alkenyl,acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity may measure inhibition of stimulation caused by a proinflammatory cytokine or other inflammatory cellular signal.

Other Reference Publication - OREF (12):
Bursten et al., The Journal of Biological Chemistry, vol. 266, No. 31, pp. 20732-20743, "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells", 1991.

US-PAT-NO: 5750575

DOCUMENT-IDENTIFIER: US 5750575 A
See image for Certificate of Correction

TITLE: Substituted amino alcohol compounds

DATE-ISSUED: May 12, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 475721

DATE FILED: June 7, 1995

PARENT-CASE:

This is a division of U.S. application Ser. No. 08/303,842, filed Sep. 8, 1994, U.S. Pat. No. 5,641,783, which is a continuation-in-part of application Ser. No. 08/152,650, filed Nov. 12, 1993, and application Ser. No. 08/164,081, filed Dec. 8, 1993, now U.S. Pat. No. 5,470,878, which are continuation-in-part application of application Ser. No. 08/040,820, filed Mar. 31, 1993, now abandoned.

US-CL-CURRENT: 514/617, 514/653 , 564/182 , 564/355 , 564/361

ABSTRACT:

Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocyle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a carbocycle comprising a substituted or unsubstituted ring system, the ring system having a single ring or two fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

18 Claims, 115 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 90

---------- KWIC --------

Detailed Description Text - DETX (2):

The invention provides a genus of compounds which can control cellular behavior by a particular phase of a secondary messenger pathway system (Bursten et al, "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

US-PAT-NO: 5670506

DOCUMENT-IDENTIFIER: US 5670506 A

TITLE: Halogen, isothiocyanate or azide substituted xanthines

DATE-ISSUED: September 23, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Leigh; Alistair	Brier	WA	N/A	N/A
Michnick; John	Seattle	WA	N/A	N/A
Kumar; Anil	Seattle	WA	N/A	N/A
Underiner; Gail	Brier	WA	N/A	N/A

APPL-NO: 08/ 042946

DATE FILED: April 5, 1993

US-CL-CURRENT: 514/141, 544/267 , 544/272 , 544/277

ABSTRACT:

There is disclosed a compound having the formula: ##STR1## wherein n is an integer from 5 to 9, wherein the core moiety is a heterocylic moiety wherein C.sub.a, C.sub.b, and C.sub.c are an R or S enantiomer or racemic mixture and the C.sub.a, C.sub.b, and C.sub.c carbon atoms are bonded together by a single bond, double bond, ether or ester linkages, wherein R.sub.1, R.sub.2 and R.sub.3 are independently halo, hydroxy, hydrogen, keto, isothiocyano, azide or haloacetoxy with the proviso that at least one of R.sub.1, R.sub.2 or R.sub.3 must be a halo, isothiocyano, azide or haloacetoxy group, wherein R.sub.4 is hydrogen, C.sub.1-6 alkyl, C.sub.1-6 alkenyl, cyclo C.sub.4-6 alkyl, or phenyl, and wherein halo refers to fluoro, chloro, bromo and iodo and salts thereof and pharmaceutical compositions thereof.

17 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 14

---------- KWIC ---------

Detailed Description Text - DETX (49):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or

other inflammatory cellular signal.

US-PAT-NO: 5641783

DOCUMENT-IDENTIFIER: US 5641783 A

TITLE: Substituted amino alcohol compounds

DATE-ISSUED: June 24, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; J. Peter	Vashon	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Kumar; Anil M.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 303842

DATE FILED: September 8, 1994

PARENT-CASE:

This application is a continuation in part of Ser. No. 08/152,650 filed Nov. 12, 1993 and continuation-in-part of Ser. No. 08/164,081, filed Dec. 8, 1993, now U.S. Pat. No. 5,470,878.

US-CL-CURRENT: 514/263.35, 514/183 , 514/222.5 , 514/223.5 , 514/224.2 , 514/226.8 , 514/227.5 , 514/228.8 , 514/229.2 , 514/230.5 , 514/230.8 , 514/237.8 , 514/241 , 514/242 , 514/243 , 514/246 , 514/247 , 514/248 , 514/249 , 514/252.16 , 514/256 , 514/259.5 , 514/264.1 , 514/266.3 , 514/270 , 514/274 , 514/297 , 514/300 , 514/301 , 514/302 , 514/303 , 514/306 , 514/307 , 514/311 , 514/312 , 514/315 , 514/345 , 514/351 , 514/357 , 514/359 , 514/360 , 514/361 , 514/362 , 514/363 , 514/364 , 514/365 , 514/367 , 514/369 , 514/372 , 514/373 , 514/374 , 514/375 , 514/376 , 514/378 , 514/379 , 514/380 , 514/381 , 514/383 , 514/389 , 514/394 , 514/395 , 514/398 , 514/399 , 514/401 , 514/404 , 514/406 , 514/413 , 514/415 , 514/416 , 514/418 , 514/423 , 514/424 , 514/425 , 514/427 , 514/428 , 544/1 , 544/162 , 544/2 , 544/215 , 544/216 , 544/219 , 544/220 , 544/224 , 544/235 , 544/239 , 544/254 , 544/255 , 544/257 , 544/262 , 544/272 , 544/277 , 544/278 , 544/280 , 544/283 , 544/286 , 544/3 , 544/301 , 544/311 , 544/335 , 544/336 , 544/350 , 544/353 , 544/385 , 544/401 , 544/53 , 544/63 , 544/65 , 544/66 , 544/67 , 544/8 , 544/90 , 544/91 , 546/102 , 546/113 , 546/114 , 546/115 , 546/117 , 546/118 , 546/119 , 546/122 , 546/138 , 546/139 , 546/150 , 546/153 , 546/157 , 546/164 , 546/176 , 546/178 , 546/242 , 546/243 , 546/246 , 546/264 , 546/300 , 546/334 , 548/100 , 548/123 , 548/125 , 548/127 , 548/128 , 548/131 , 548/134 , 548/146 , 548/153 , 548/179 , 548/186 , 548/207 , 548/214 , 548/215 , 548/217 , 548/221 , 548/225 , 548/228 , 548/229 , 548/235 , 548/237 , 548/240 , 548/241 , 548/243 , 548/247 , 548/252 , 548/267.2 , 548/267.8 , 548/303.7 , 548/306.4 , 548/307.1 , 548/309.7 , 548/319.1 , 548/323.5 , 548/340.1 , 548/348.1 , 548/349.1 , 548/356.1 , 548/370.1 , 548/375.1 , 548/379.4 , 548/452 , 548/453 , 548/470 , 548/482 , 548/485 , 548/486 , 548/491 , 548/503 , 548/532 , 548/543 , 548/546 , 548/550 , 548/565 , 548/566

ABSTRACT:

Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocycle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a terminal moiety comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

22 Claims, 115 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 88

---------- KWIC ---------

Detailed Description Text - DETX (2):

The invention provides a genus of compounds which can control cellular behavior by a particular phase of a secondary messenger pathway system (Bursten et al., "Interleukin-1 Rapidly Stimulates Lysophosphatidate Acyltransferase and Phosphatidate Phosphohydrolase Activities in Human Mesangial Cells," J. Biol. Chem., Vol. 266, No. 31, pages 20732-20743, Nov. 5, 1991). The second messengers are lipids or phospholipids and use the following abbreviations:

US-PAT-NO: 5521315

DOCUMENT-IDENTIFIER: US 5521315 A

TITLE: Olefin substituted long chain compounds

DATE-ISSUED: May 28, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Underiner; Gail	Brier	WA	N/A	N/A
Porubek; David	Seattle	WA	N/A	N/A
Klein; J. Peter	Vashon	WA	N/A	N/A
Eiseman; Elisa	Seattle	WA	N/A	N/A
Leigh; Alistair	Brier	WA	N/A	N/A
Kumar; Anil	Seattle	WA	N/A	N/A
Michnick; John	Seattle	WA	N/A	N/A

APPL-NO: 08/ 059697

DATE FILED: May 10, 1993

PARENT-CASE:

CROSS REFERENCE TO RELATED PATENT APPLICATION

This application is a continuation-in-part application from U.S. patent application Ser. No. 08/003,372 filed Jan. 12, 1993 now U.S. Pat. No. 5,354,756.

US-CL-CURRENT: 546/243, 544/285 , 546/242

ABSTRACT:

There is disclosed an olefin-substituted compound having the formula:

R--(core moiety),

wherein R is a straignt chain hydrocarbon having at least one double bond and a carbon chain length of from about 6 to about 18 carbon atoms, wherein multiple double bonds are separated from each other by at least three carbon atoms, wherein the closest double bond to the core moiety is at least five carbon atoms from the core moiety, and wherein the hydrocarbon chain may be substituted by a hydroxyl, halo, keto or dimethylanimo group and/or interrupted by an oxygen atom and salts thereof and pharmaceutical compositions thereof.

7 Claims, 22 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 22

---------- KWIC ---------

Detailed Description Text - DETX (39):
IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase

(LPAAT) and phosphatidate phosphohydrolase within 5 seconds of cell (for example, human mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at the inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

US-PAT-NO: 5470878

DOCUMENT-IDENTIFIER: US 5470878 A

TITLE: Cell signaling inhibitors

DATE-ISSUED: November 28, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Michnick; John	Seattle	WA	N/A	N/A
Underiner; Gail E.	Brier	WA	N/A	N/A
Klein; J. Peter	Vashon Island	WA	N/A	N/A
Rice; Glenn C.	Seattle	WA	N/A	N/A

APPL-NO: 08/ 164081

DATE FILED: December 8, 1993

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION

This application is a Continuation-in-Part Application of U.S. application Ser. No. 08/040,820 filed Mar. 31, 1993, now abandoned.

US-CL-CURRENT: 514/558, 514/274 , 514/299 , 514/315 , 514/418 , 514/425 , 514/529 , 514/552 , 514/561 , 514/613 , 514/617 , 514/626 , 514/629 , 514/669 , 544/254 , 544/285 , 544/301 , 546/183 , 546/243 , 548/486 , 548/556

ABSTRACT:

Therapeutic compounds have the formula:

(X)j-(non-cyclic core moiety),

j being an integer from one to three, the core moiety is non-cyclic and X is a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of: ##STR1## *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3. Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms. r and s are independently integers

from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxy group.

10 Claims, 43 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 42

---------- KWIC ---------

Detailed Description Text - DETX (40):

IL-1 activates (through the Type I IL-1 receptor) a lyso-PA acyltransferase (LPAAT) and **phosphatidate phosphohydrolase within 5 seconds of cell (for example, human** mesangial cells, HMC) exposure to this cytokine. Activation of both enzymes results in production of PA species with sn-1 and sn-2 unsaturated acyl groups, with the majority of sn-2 acyl chains being polyunsaturated. Both IL-1 and a product of LPAAT, 1,2-sn-dilinoleoyl PA, activate a signaling pathway involving hydrolysis of PE to PA. This reaction is followed by dephosphorylation of PA to produce both 1,2-sn-diacylglycerol, and 1-o-alkyl or 1-o-alkenyl acylglycerol (AAG) species. The inventive compounds exert their activity by inhibiting one or both enzymes at an inner leaflet of the plasma membrane. Therefore, appropriate in vitro models for drug activity is to measure inhibition of stimulation caused by a pro-inflammatory cytokine or other inflammatory cellular signal.

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  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:39:22 ON 01 JUN 2005

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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 09:39:39 ON 01 JUN 2005
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

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       1332899 ACID
        108109 PHOSPHATASE#
           104 PHOSPHATIDIC ACID PHOSPHATASE#
                 (PHOSPHATIDIC(W)ACID(W)PHOSPHATASE#)
           997 PHOSPHATIDATE
          6623 PHOSPHOHYDROLASE#
           356 PHOSPHATIDATE PHOSPHOHYDROLASE#
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L1         458 PHOSPHATIDIC ACID PHOSPHATASE# OR PHOSPHATIDATE PHOSPHOHYDROLASE
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           843 PHOSPHATIDATE
          1671 PHOSPHOHYDROLASE#
           447 PHOSPHATIDATE PHOSPHOHYDROLASE#
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            66 PHOSPHATIDATE PHOSPHOHYDROLASE#
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                (PHOSPHATIDATE(W)PHOSPHOHYDROLASE#)
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          112777 PHOSPHATASE#
             169 PHOSPHATIDIC ACID PHOSPHATASE#
                   (PHOSPHATIDIC(W)ACID(W)PHOSPHATASE#)
            1068 PHOSPHATIDATE
            2442 PHOSPHOHYDROLASE#
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L6           419 PHOSPHATIDIC ACID PHOSPHATASE# OR PHOSPHATIDATE PHOSPHOHYDROLASE
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            1836 PHOSPHATIDATE
            2635 PHOSPHOHYDROLASE#
             485 PHOSPHATIDATE PHOSPHOHYDROLASE#
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L7           709 PHOSPHATIDIC ACID PHOSPHATASE# OR PHOSPHATIDATE PHOSPHOHYDROLASE
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               0 PHOSPHATIDIC ACID PHOSPHATASE#
                   (PHOSPHATIDIC(W)ACID(W)PHOSPHATASE#)
               1 PHOSPHATIDATE
               8 PHOSPHOHYDROLASE#
               0 PHOSPHATIDATE PHOSPHOHYDROLASE#
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L8             0 PHOSPHATIDIC ACID PHOSPHATASE# OR PHOSPHATIDATE PHOSPHOHYDROLASE
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TOTAL FOR ALL FILES
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        678273 PURIF?
L13         32 L1 (10A)(ISOLAT? OR PURIF?)

FILE 'SCISEARCH'
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        244631 PURIF?
L14         28 L2 (10A)(ISOLAT? OR PURIF?)

FILE 'LIFESCI'
        288428 ISOLAT?
        114431 PURIF?
L15          9 L3 (10A)(ISOLAT? OR PURIF?)

FILE 'BIOTECHDS'
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         66925 PURIF?
L16          4 L4 (10A)(ISOLAT? OR PURIF?)

FILE 'BIOSIS'
        815176 ISOLAT?
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L17         29 L5 (10A)(ISOLAT? OR PURIF?)

FILE 'EMBASE'
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L18         26 L6 (10A)(ISOLAT? OR PURIF?)

FILE 'HCAPLUS'
       1036022 ISOLAT?
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L19         45 L7 (10A)(ISOLAT? OR PURIF?)

FILE 'NTIS'
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         11932 PURIF?
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FILE 'ESBIOBASE'
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FILE 'BIOTECHNO'
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L22         14 L10(10A)(ISOLAT? OR PURIF?)

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FILE 'SCISEARCH'
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L26         27 L2 (10A)HUMAN

FILE 'LIFESCI'
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L27          9 L3 (10A)HUMAN

FILE 'BIOTECHDS'
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FILE 'BIOSIS'
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FILE 'EMBASE'
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FILE 'ESBIOBASE'
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L33          10 L9 (10A)HUMAN

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FILE 'WPIDS'
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=> s l12(10a)gene/q
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FILE 'SCISEARCH'
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FILE 'LIFESCI'
L39           7 L3 (10A)GENE/Q

FILE 'BIOTECHDS'
L40           6 L4 (10A)GENE/Q

FILE 'BIOSIS'
L41          15 L5 (10A)GENE/Q

FILE 'EMBASE'
L42           7 L6 (10A)GENE/Q

FILE 'HCAPLUS'
L43          53 L7 (10A)GENE/Q

FILE 'NTIS'
L44           0 L8 (10A)GENE/Q

FILE 'ESBIOBASE'
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FILE 'BIOTECHNO'
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FILE 'WPIDS'
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TOTAL FOR ALL FILES
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L49          45 (L13 OR L25 OR L37) NOT 1998-2005/PY

FILE 'SCISEARCH'
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L50          39 (L14 OR L26 OR L38) NOT 1998-2005/PY

FILE 'LIFESCI'
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L51          14 (L15 OR L27 OR L39) NOT 1998-2005/PY
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L53          47 (L17 OR L29 OR L41) NOT 1998-2005/PY

FILE 'EMBASE'
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L54          36 (L18 OR L30 OR L42) NOT 1998-2005/PY

FILE 'HCAPLUS'
       7095138 1998-2005/PY
L55          62 (L19 OR L31 OR L43) NOT 1998-2005/PY

FILE 'NTIS'
        141998 1998-2005/PY
L56           0 (L20 OR L32 OR L44) NOT 1998-2005/PY

FILE 'ESBIOBASE'
       2137379 1998-2005/PY
L57           6 (L21 OR L33 OR L45) NOT 1998-2005/PY

FILE 'BIOTECHNO'
        724097 1998-2005/PY
L58          20 (L22 OR L34 OR L46) NOT 1998-2005/PY

FILE 'WPIDS'
       5979817 1998-2005/PY
L59           0 (L23 OR L35 OR L47) NOT 1998-2005/PY

TOTAL FOR ALL FILES
L60         269 (L24 OR L36 OR L48) NOT 1998-2005/PY

=> dup rem l60
PROCESSING COMPLETED FOR L60
L61           89 DUP REM L60 (180 DUPLICATES REMOVED)

=> d 1-
YOU HAVE REQUESTED DATA FROM 89 ANSWERS - CONTINUE? Y/(N):y

L61  ANSWER 1 OF 89     MEDLINE on STN                  DUPLICATE 1
TI   Cloning and characterization of two human isozymes of
     Mg2+-independent phosphatidic acid phosphatase
     .
SO   Journal of biological chemistry, (1997 Sep 26) 272 (39) 24572-8.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Kai M; Wada I; Imai S i; Sakane F; Kanoh H
AN   97450990     MEDLINE

L61  ANSWER 2 OF 89     MEDLINE on STN                  DUPLICATE 2
TI   Erythromycin A-derived macrolides modify the functional activities of
     human neutrophils by altering the phospholipase D-
     phosphatidate phosphohydrolase transduction pathway:
     L-cladinose is involved both in alterations of neutrophil functions and
     modulation of this transductional pathway.
SO   Journal of immunology (Baltimore, Md. : 1950), (1997 Oct 15) 159 (8)
     3995-4005.
     Journal code: 2985117R. ISSN: 0022-1767.
AU   Abdelghaffar H; Vazifeh D; Labro M T
AN   1998018262     MEDLINE

L61  ANSWER 3 OF 89  SCISEARCH  COPYRIGHT (c) 2005 The Thomson Corporation  on
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STN
TI Two **human** type 2 **phosphatidic acid phosphatase** isozymes
SO FASEB JOURNAL, (31 JUL 1997) Vol. 11, No. 9, Supp. [S], pp. 2847-2847. Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0892-6638.
AU Kai M (Reprint); Wada I; Kanoh H
AN 1998:408315 SCISEARCH

L61 ANSWER 4 OF 89 MEDLINE on STN DUPLICATE 3
TI An unexpected structural relationship between integral membrane phosphatases and soluble haloperoxidases.
SO Protein science : a publication of the Protein Society, (1997 Aug) 6 (8) 1764-7.
Journal code: 9211750. ISSN: 0961-8368.
AU Neuwald A F
AN 97406916 MEDLINE

L61 ANSWER 5 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Two **human** type 2 **phosphatidic acid phosphatase** isozymes.
SO FASEB Journal, (1997) Vol. 11, No. 9, pp. A1344.
Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology. San Francisco, California, USA. August 24-29, 1997.
CODEN: FAJOEC. ISSN: 0892-6638.
AU Kai, M.; Wada, I.; Kanoh, H.
AN 1997:422112 BIOSIS

L61 ANSWER 6 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Identification of **phosphatidic acid phosphatase** type 2 (PAP-2) as an androgen-regulated **gene** in the human prostatic adenocarcinoma cell line LNCaP.
SO Steroids, (Nov., 1997) Vol. 62, No. 11, pp. 735. print.
Meeting Info.: XVIII Meeting of the International Study Group for Steroid Hormones. Rome, Italy. November 29-December 2, 1997. International Study Group for Steroid Hormones.
CODEN: STEDAM. ISSN: 0039-128X.
AU Ulrix, W.; Swinnen, J.; Heyns, W.; Verhoeven, G.
AN 1998:103298 BIOSIS

L61 ANSWER 7 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 4
TI Effects of hesperidine, naringin and their aglycones on the in vitro activity of **phosphatidate phosphohydrolase**, and on the proliferation and growth in cultured **human** hepatocytes HepG2 cells.
SO Agricultural Chemistry and Biotechnology, (Dec., 1997) Vol. 40, No. 6, pp. 577-582. print.
CODEN: JKACA7. ISSN: 0368-2897.
AU Cha, Jae-Young; Cho, Young-Su [Reprint author]
AN 1998:119820 BIOSIS

L61 ANSWER 8 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Metabolism and possible compartmentalization of inositol lipids in isolated rat-liver nuclei
SO Biochemical Journal (1997), 327(2), 569-576
CODEN: BIJOAK; ISSN: 0264-6021
AU Vann, Lewis R.; Wooding, F. B. Peter; Irvine, Robin F.; Divecha, Nullin
AN 1997:709300 HCAPLUS
DN 128:31505

L61 ANSWER 9 OF 89 MEDLINE on STN DUPLICATE 5
TI Identification and cDNA cloning of 35-kDa phosphatidic acid phosphatase (type 2) bound to plasma membranes. Polymerase chain reaction amplification of mouse H2O2-inducible hic53 clone yielded the cDNA encoding phosphatidic acid phosphatase.
SO Journal of biological chemistry, (1996 Aug 2) 271 (31) 18931-8.
Journal code: 2985121R. ISSN: 0021-9258.
AU Kai M; Wada I; Imai S; Sakane F; Kanoh H
AN 96324980 MEDLINE

L61 ANSWER 10 OF 89 MEDLINE on STN DUPLICATE 6
TI Phosphatidate phosphohydrolase catalyzes the hydrolysis of ceramide 1-phosphate, lysophosphatidate, and sphingosine 1-phosphate.
SO Journal of biological chemistry, (1996 Jul 12) 271 (28) 16506-9.
Journal code: 2985121R. ISSN: 0021-9258.
AU Waggoner D W; Gomez-Munoz A; Dewald J; Brindley D N
AN 96279213 MEDLINE

L61 ANSWER 11 OF 89 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 7
TI Regulation of phosphatidate phosphatase activity from the yeast Saccharomyces cerevisiae by phospholipids
SO BIOCHEMISTRY (WASH.), (1996) vol. 35, no. 12, pp. 3790-3796.
ISSN: 0006-2960.
AU Wu, Wen-I; Carman, G.M.*
AN 97:2290 LIFESCI

L61 ANSWER 12 OF 89 MEDLINE on STN DUPLICATE 8
TI Identification of **phosphatidate phosphohydrolase purified** from rat liver membranes on SDS-polyacrylamide gel electrophoresis.
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Journal code: 0155157. ISSN: 0014-5793.
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AN 96176315 MEDLINE

L61 ANSWER 13 OF 89 MEDLINE on STN DUPLICATE 9
TI **Purification** and characterization of novel plasma membrane **phosphatidate phosphohydrolase** from rat liver.
SO Journal of biological chemistry, (1995 Aug 18) 270 (33) 19422-9.
Journal code: 2985121R. ISSN: 0021-9258.
AU Waggoner D W; Martin A; Dewald J; Gomez-Munoz A; Brindley D N
AN 95370279 MEDLINE

L61 ANSWER 14 OF 89 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 10
TI A PHOSPHOLIPASE D-MEDIATED PATHWAY FOR GENERATING DIACYLGLYCEROL IN NUCLEI FROM MADIN-DARBY CANINE KIDNEY-CELLS
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (19 MAY 1995) Vol. 270, No. 20, pp. 11738-11740.
ISSN: 0021-9258.
AU BALBOA M A; BALSINDE J; DENNIS E A; INSEL P A (Reprint)
AN 95:350291 SCISEARCH

L61 ANSWER 15 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Identification of type-2 phosphatidic acid phosphohydrolase (PAPH-2) in neutrophil plasma membranes
SO Cellular Signalling (1994), 6(8), 933-41
CODEN: CESIEY; ISSN: 0898-6568
AU Boder, Eric; Taylor, Greg; Akard, Luke; Jansen, Jan; English, Denis
AN 1995:424654 HCAPLUS
DN 122:210388

L61 ANSWER 16 OF 89 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

TI INCREASED ACTIVITY OF **PHOSPHATIDATE PHOSPHOHYDROLASE** IN **HUMAN** COLORECTAL TUMORS
SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1994) Supp. 18D, pp. 60. ISSN: 0730-2312.
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AN 94:275051 SCISEARCH

L61 ANSWER 17 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Increased activity of **phosphatidate phosphohydrolase** in **human** colorectal tumours.
SO Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18D, pp. 60.
Meeting Info.: Keystone Symposium on Lipid Second Messengers. Taos, New Mexico, USA. February 26-March 4, 1994.
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L61 ANSWER 18 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI The role of phosphatidic acid phosphohydrolase in human neutrophil signal transduction
SO (1993) 214 pp. Avail.: Univ. Microfilms Int., Order No. DA9415100
From: Diss. Abstr. Int. B 1994, 54(12, Pt. 1), 6187
AU Perry, David Kenneth
AN 1994:532183 HCAPLUS
DN 121:132183

L61 ANSWER 19 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI A novel ecto-phosphatidic acid phosphohydrolase activity mediates activation of neutrophil superoxide generation by exogenous phosphatidic acid
SO Journal of Biological Chemistry (1993), 268(34), 25302-10
CODEN: JBCHA3; ISSN: 0021-9258
AU Perry, David K.; Stevens, Victoria L.; Widlanski, Theodore S.; Lambeth, J. David
AN 1993:624002 HCAPLUS
DN 119:224002

L61 ANSWER 20 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Decreased activities of phosphatidate phosphohydrolase and phospholipase D in ras and tyrosine kinase (fps) transformed fibroblasts
SO Journal of Biological Chemistry (1993), 268(32), 23924-32
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AN 1993:600471 HCAPLUS
DN 119:200471

L61 ANSWER 21 OF 89 MEDLINE on STN DUPLICATE 11
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Journal code: 8302946. ISSN: 0270-9139.
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AN 94010748 MEDLINE

L61 ANSWER 22 OF 89 MEDLINE on STN DUPLICATE 12
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Journal code: 0404375. ISSN: 0036-5513.
AU Humble E; Berglund L
AN 94023775 MEDLINE

L61 ANSWER 23 OF 89 MEDLINE on STN DUPLICATE 13
TI Differential properties of phosphatidate phosphohydrolase and diacylglyceride lipase activities in retinal subcellular fractions and rod outer segments.
SO Comparative biochemistry and physiology. B, Comparative biochemistry, (1993 Jan) 104 (1) 141-8.
Journal code: 2984730R. ISSN: 0305-0491.
AU Pasquare S J; Giusto N M
AN 93193415 MEDLINE

L61 ANSWER 24 OF 89 MEDLINE on STN DUPLICATE 14
TI Low concentration of Triton X-100 inhibits diacylglycerol acyltransferase without measurable effect on **phosphatidate phosphohydrolase** in the **human** primordial placenta.
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Journal code: 8309201. ISSN: 0231-424X.
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L61 ANSWER 25 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
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SO Biochimica et Biophysica Acta (1993), 1169(1), 25-9
CODEN: BBACAQ; ISSN: 0006-3002
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DN 119:136385

L61 ANSWER 26 OF 89 MEDLINE on STN DUPLICATE 15
TI **Purification** and properties of **phosphatidic acid phosphatase** from porcine thymus membranes.
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Journal code: 2985121R. ISSN: 0021-9258.
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AN 93094244 MEDLINE

L61 ANSWER 27 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Role of phospholipase D-derived diradylglycerol in the activation of the human neutrophil respiratory burst oxidase. Inhibition by phosphatidic acid phosphohydrolase inhibitors
SO Journal of Immunology (1992), 149(8), 2749-58
CODEN: JOIMA3; ISSN: 0022-1767
AU Perry, David K.; Hand, W. Lee; Edmondson, Dale E.; Lambeth, J. David
AN 1993:122904 HCAPLUS
DN 118:122904

L61 ANSWER 28 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Regulation of phosphatidic acid phosphohydrolase activity during stimulation of human polymorphonuclear leukocytes
SO FASEB Journal (1992), 6(9), 2720-5
CODEN: FAJOEC; ISSN: 0892-6638
AU Truett, A. P., III; Bocckino, S. B.; Murray, J. J.
AN 1992:468339 HCAPLUS
DN 117:68339

L61 ANSWER 29 OF 89 MEDLINE on STN DUPLICATE 16
TI Vanadate-sensitive **phosphatidate phosphohydrolase** activity in a **purified** rabbit kidney Na,K-ATPase preparation.
SO Biochimica et biophysica acta, (1992 Jun 11) 1107 (1) 143-9.
Journal code: 0217513. ISSN: 0006-3002.

AU Swarts H G; Moes M; Schuurmans Stekhoven F M; De Pont J J
AN 92314021 MEDLINE

L61 ANSWER 30 OF 89 MEDLINE on STN DUPLICATE 17
TI Interleukin-1 rapidly stimulates lysophosphatidate acyltransferase and **phosphatidate phosphohydrolase** activities in **human** mesangial cells.
SO Journal of biological chemistry, (1991 Nov 5) 266 (31) 20732-43.
Journal code: 2985121R. ISSN: 0021-9258.
AU Bursten S L; Harris W E; Bomsztyk K; Lovett D
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L61 ANSWER 31 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI De novo synthesis of diacylglycerol from glucose. A new pathway of signal transduction in human neutrophils stimulated during phagocytosis of β-glucan particles
SO Journal of Biological Chemistry (1991), 266(13), 8034-8
CODEN: JBCHA3; ISSN: 0021-9258
AU Rossi, Filippo; Grzewkowiak, Miroslawa; Della Bianca, Vittorina; Sharbati, Andrea
AN 1991:245819 HCAPLUS
DN 114:245819

L61 ANSWER 32 OF 89 MEDLINE on STN DUPLICATE 18
TI Sphingosine inhibits **phosphatidate phosphohydrolase** in **human** neutrophils by a protein kinase C-independent mechanism.
SO Journal of biological chemistry, (1991 Feb 5) 266 (4) 2013-6.
Journal code: 2985121R. ISSN: 0021-9258.
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AN 91115804 MEDLINE

L61 ANSWER 33 OF 89 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 19
TI LIPID BREAKDOWN IN SMOOTH MICROSOMAL-MEMBRANES FROM BEAN COTYLEDONS ALTERS MEMBRANE-PROTEINS AND INDUCES PROTEOLYSIS
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AN 91:68554 SCISEARCH

L61 ANSWER 34 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI REGULATION OF **HUMAN PHOSPHATIDATE PHOSPHOHYDROLASE** IN **HUMAN** LIVER.
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AN 1992:86892 BIOSIS

L61 ANSWER 35 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
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SO FASEB Journal, (1990) Vol. 4, No. 7, pp. A2060.
Meeting Info.: JOINT MEETING OF THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, AND THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, NEW ORLEANS, LOUISIANA, USA, JUNE 4-7, 1990. FASEB (FED AM SOC EXP BIOL) J.
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AN 1990:346613 BIOSIS

L61 ANSWER 36 OF 89 MEDLINE on STN DUPLICATE 20
TI Properties of **phosphatidate phosphohydrolase** and diacylglycerol acyltransferase activities in the **isolated** rat heart. Effect of glucagon, ischaemia and diabetes.
SO Biochemical journal, (1990 Jun 1) 268 (2) 487-92.
Journal code: 2984726R. ISSN: 0264-6021.
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L61 ANSWER 37 OF 89 MEDLINE on STN DUPLICATE 21
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Journal code: 7509386. ISSN: 0253-1801.
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AN 91368151 MEDLINE

L61 ANSWER 38 OF 89 MEDLINE on STN DUPLICATE 22
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SO Journal of biological chemistry, (1989 Oct 15) 264 (29) 17069-77.
Journal code: 2985121R. ISSN: 0021-9258.
AU Billah M M; Eckel S; Mullmann T J; Egan R W; Siegel M I
AN 90008859 MEDLINE

L61 ANSWER 39 OF 89 MEDLINE on STN DUPLICATE 23
TI Apparent lack of effect of obesity on the soluble **phosphatidic acid phosphatase** activity in **human** adipose tissue.
SO Lipids, (1989 Dec) 24 (12) 1048-52.
Journal code: 0060450. ISSN: 0024-4201.
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L61 ANSWER 40 OF 89 MEDLINE on STN DUPLICATE 24
TI Rat adipose tissue phosphatidic acid phosphatase: lack of effect of nucleotides on cytosolic enzyme activity.
SO Acta chemica Scandinavica (Copenhagen, Denmark : 1989), (1989 Aug) 43 (7) 680-3.
Journal code: 9012772. ISSN: 0904-213X.
AU al-Shurbaji A; Berglund L
AN 91058841 MEDLINE

L61 ANSWER 41 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Phospholipase D activation is functionally linked to superoxide generation in the human neutrophil
SO Biochemical Journal (1989), 264(2), 617-20
CODEN: BIJOAK; ISSN: 0306-3275
AU Bonser, Robert W.; Thompson, Neil T.; Randall, Roger W.; Garland, Lawrence G.
AN 1990:19837 HCAPLUS
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L61 ANSWER 42 OF 89 MEDLINE on STN DUPLICATE 25
TI **Phosphatidate phosphohydrolase** in **purified** rat brain myelin.
SO Journal of neuroscience research, (1989 Nov) 24 (3) 431-6.
Journal code: 7600111. ISSN: 0360-4012.
AU Vaswani K K; Ledeen R W
AN 90080028 MEDLINE

L61 ANSWER 43 OF 89 MEDLINE on STN DUPLICATE 26

TI Activation of rat liver cytosolic phosphatidic acid phosphatase by nucleoside diphosphates.
SO Biochimica et biophysica acta, (1989 Apr 26) 1002 (3) 382-7.
Journal code: 0217513. ISSN: 0006-3002.
AU Berglund L; Bjorkhem I; Angelin B; Einarsson K
AN 89229186 MEDLINE

L61 ANSWER 44 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI MECHANISM OF ACTION OF BILE ACID SEQUESTRANTS AND OTHER LIPID-LOWERING DRUGS.
SO Cardiology, (1989) Vol. 76, No. SUPPL. 1, pp. 65-74.
Meeting Info.: WORKSHOP ON A NEW ERA OF LIPID-LOWERING DRUG ALTERNATIVES, LAGUNA NIGUEL, CALIFORNIA, USA. CARDIOLOGY.
CODEN: CAGYAO. ISSN: 0008-6312.
AU SHEPHERD J [Reprint author]
AN 1989:349858 BIOSIS

L61 ANSWER 45 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI MEMBRANE-BOUND PHOSPHATASES IN ESCHERICHIA-COLI SEQUENCE OF THE PGP-B GENE AND DUAL SUBCELLULAR LOCALIZATION OF THE PGP-B PRODUCT.
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CODEN: JOBAAY. ISSN: 0021-9193.
AU ICHO T [Reprint author]
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L61 ANSWER 46 OF 89 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
TI The phosphatidylcholine pathway of diacylglycerol formation stimulated by phorbol diesters occurs via phospholipase D activation
SO FEBS Letters, (1988), 233/1 (153-157)
CODEN: FEBLAL ISSN: 0014-5793
AU Cabot M.C.; Welsh C.J.; Cao H.; Chabbott H.
AN 1988:18149964 BIOTECHNO

L61 ANSWER 47 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Accumulation of triacylglycerol in human fetal organs
SO Indian Journal of Medical Research (1913-1988) (1987), 86(Sept.), 401-9
CODEN: IJMRAQ; ISSN: 0019-5340
AU Chandra, Nimai Chand; Bhattacharyya, Reba; Samanta, Bimal Krishna; Dutta, Gita; Mukherjee, Kanailal
AN 1987:633732 HCAPLUS
DN 107:233732

L61 ANSWER 48 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI A rapid assay for measuring the activity and the magnesium and calcium requirements of phosphatidate phosphohydrolase in cytosolic and microsomal fractions of rat liver
SO Biochemical Journal (1987), 245(2), 347-55
CODEN: BIJOAK; ISSN: 0306-3275
AU Martin, Ashley; Hales, Paul; Brindley, David N.
AN 1987:492412 HCAPLUS
DN 107:92412

L61 ANSWER 49 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
TI The magnesium(2+)-dependent phosphatidate phosphohydrolase of rat lung
SO (1986) No pp. Given Avail.: NLC
From: Diss. Abstr. Int. B 1986, 47(5), 1976
AU Walton, Paul Albert
AN 1987:46204 HCAPLUS
DN 106:46204

L61 ANSWER 50 OF 89 HCAPLUS COPYRIGHT 2005 ACS on STN
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between cytosol and endoplasmic reticulum in a permanent cell line from human lung
SO Biochemistry and Cell Biology (1986), 64(11), 1135-40
CODEN: BCBIEQ; ISSN: 0829-8211
AU Walton, Paul A.; Possmayer, Fred
AN 1986:588472 HCAPLUS
DN 105:188472

L61 ANSWER 51 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 27
TI LIPID COMPOSITION OF PLASMA MEMBRANES AND TONOPLASTS ISOLATED FROM ETIOLATED SEEDLINGS OF MUNG BEAN VIGNA-RADIATA.
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AU YOSHIDA S [Reprint author]; UEMURA M
AN 1987:83039 BIOSIS

L61 ANSWER 52 OF 89 MEDLINE on STN DUPLICATE 28
TI **Isolation** and characterization of multiple forms of Mg2+-dependent **phosphatidate phosphohydrolase** from rat adipose cytosol.
SO Biochimica et biophysica acta, (1986 Sep 12) 878 (2) 225-37.
Journal code: 0217513. ISSN: 0006-3002.
AU Wells G N; Osborne L J; Jamdar S C
AN 87000664 MEDLINE

L61 ANSWER 53 OF 89 MEDLINE on STN DUPLICATE 29
TI Phosphatidate phosphatase activity in isolated rod outer segment from bovine retina.
SO Biochimica et biophysica acta, (1986 Feb 12) 875 (2) 195-202.
Journal code: 0217513. ISSN: 0006-3002.
AU Pasquare de Garcia S J; Giusto N M
AN 86104365 MEDLINE

L61 ANSWER 54 OF 89 MEDLINE on STN DUPLICATE 30
TI Insulin antagonises the growth hormone-mediated increase in the activity of **phosphatidate phosphohydrolase** in **isolated** rat hepatocytes.
SO FEBS letters, (1986 Jun 23) 202 (1) 133-6.
Journal code: 0155157. ISSN: 0014-5793.
AU Pittner R A; Bracken P; Fears R; Brindley D N
AN 86248068 MEDLINE

L61 ANSWER 55 OF 89 MEDLINE on STN DUPLICATE 31
TI Spermine antagonises the effects of dexamethasone, glucagon and cyclic AMP in increasing the activity of **phosphatidate phosphohydrolase** in **isolated** rat hepatocytes.
SO FEBS letters, (1986 Oct 20) 207 (1) 42-6.
Journal code: 0155157. ISSN: 0014-5793.
AU Pittner R A; Bracken P; Fears R; Brindley D N
AN 87030901 MEDLINE

L61 ANSWER 56 OF 89 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI **PURIFICATION** AND CHARACTERIZATION OF **PHOSPHATIDATE PHOSPHOHYDROLASE** FROM RAT EPIDIDYMAL FAT
SO FEDERATION PROCEEDINGS, (1985) Vol. 44, No. 5, pp. 1787.
AU WELLS G N (Reprint); JAMDAR S C; OSBORNE L J
AN 85:178528 SCISEARCH

L61 ANSWER 57 OF 89 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI THE CHARACTERIZATION OF **PURIFIED** MG-2&-DEPENDENT **PHOSPHATIDATE PHOSPHOHYDROLASES** (PPH) FROM RAT ADIPOSE

CYTOSOL
SO FEDERATION PROCEEDINGS, (1985) Vol. 44, No. 5, pp. 1787.
AU JAMDAR S C (Reprint); WELLS G N; OSBORNE L J
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L61 ANSWER 58 OF 89 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
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